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STUDIES ON THE HUMAN NEUROMUSCULAR MECHANISM

II. EFFECT OF VENTROMEDIAL CHORDOTOMY ON MUSCULAR SPASTICITY IN MAN

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CHICAGO

Decerebrate rigidity in the cat has much in common with the spastic paralysis which results from cerebral lesions in man. It is thus natural that an endeavor should be made to confirm the findings in the lower animal by appropriate investigations in man and that attempts should be made to convert the results of experiments in the laboratory into therapeutic procedures of value in the clinic. The present paper is the report of such an attempt.

It has long been known that appropriate transection of the brain stem gives rise to the condition known as decerebrate rigidity, a condition characterized by extensor rigidity and enhancement of the stretch reflex and the tendon reflexes, e. g., the knee jerk, as well as other alterations in the reflex activities of the skeletal muscles. Although such transections are, for the sake of convenience, usually made through the mesencephalon in the region of the corpora quadrigemina, a similar picture of extensor rigidity can be obtained by transecting the brain stem caudal to that level at any point above the vestibular nuclei. Transections below these nuclei result in an entirely different picture, characterized by flaccidity of the skeletal musculature, increased susceptibility of the reflexes to inhibition, diminution or abolition of the stretch reflex and prolongation of the knee jerk (due to the fact that in the acute spinal state only the slower red muscle fibers respond in the knee jerk). This condition is also the typical result of transecting the spinal cord.[1] It is obvious that the vestibular nuclei or some other mechanism in the same neighborhood is essential for the maintenance

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1. Ballif, L.; Fulton, J. F., and Liddell, E. G. T.: Observations on Spinal and Decerebrate Knee-Jerks with Special Reference to Their Inhibition by Single Break Shocks, Proc. Roy. Soc., London, s.B **98**:589-607, 1925.

of decerebrate rigidity in the cat. That it is the vestibular nuclei and their spinal projections which are so concerned was clearly shown by the skilfully executed experiments of Fulton, Liddell and Rioch.[2]

By selective section of various columns of the spinal cord, these authors sought to determine which tracts are responsible for the maintenance of decerebrate extensor rigidity and which, when severed in a decerebrate cat, would transform the knee jerk from one of relatively short duration (from 40 to 60 sigmas) and resistant to inhibitory stimuli to one characteristic of the spinal preparation, of long duration (about 100 sigmas) and susceptible to inhibitory impulses. They found this tract to be localized in the anteromedial columns of the spinal cord, and as the most important tract in this region is the vestibulospinal pathway, it seemed likely that this was the one concerned. They next directed their attention to destroying this tract at its origin, the vestibular nuclei. Small unilateral lesions were made in the floor of the fourth ventricle. Two sets of experiments were performed, acute and chronic. In the acute preparations the lesions in the floor of the fourth ventricle were made in acutely decerebrated cats. When the lesions destroyed the vestibular nuclei, particularly Deiters' nucleus, on one side there occurred an immediate and striking reduction in the extensor rigidity in the extremities on the same side as the damaged nuclei. Such an animal when held on its back exhibited rigidly extended forelimbs and hindlimbs on the side opposite the lesion (typical of decerebrate rigidity), while the limbs on the same side as the lesion in the medulla oblongata were flaccid and rested in a flexed position against the body. The stretch reflex in the quadriceps extensor muscles was diminished or absent, and the ipsilateral knee jerk was pendular, prolonged and more readily inhibited than that on the opposite side.

In the chronic preparations unilateral destruction of the vestibular nuclei was carried out aseptically, and the animals were permitted to survive three weeks before they were decerebrated. Prior to decerebration these animals exhibited the nystagmus, rolling movements and asymmetry of posture characteristic of those with vestibular lesions. Furthermore, there was marked "hypotonia" of the ipsilateral extremities. After decerebration "good extensor rigidity developed," but it was less marked on the side on which the vestibular nuclei had been damaged. Other changes in the stretch reflex and the knee jerk similar in type, though not in degree, to those seen after transection of the spinal cord and in the animals previously referred to in which the anteromedial column of the spinal cord was sectioned were also observed.

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2. Fulton, J. F.; Liddell, E. G. T., and Rioch, D. M.: The Influence of Experimental Lesions of the Spinal Cord upon the Knee Jerks: I. Acute Lesions, Brain **53**:311-326, 1930; The Influence of Unilateral Destruction of the Vestibular Nuclei upon Posture and the Knee-Jerk, ibid. **53**:327-343, 1930.

From these observations, Fulton and his co-workers logically concluded that the vestibular nuclei and the vestibulospinal tract constitute the mechanism necessary for maintenance of the extensor rigidity called forth by decerebration, although they considered it likely that other centers contribute less importantly to the same end.

In view of this clear demonstration of the importance of the vestibulospinal tract in maintenance of the extensor rigidity of decerebration and of the ipsilateral flaccidity which results either from severance of the tract or from destruction of its nuclei, it seemed that section of the anteromedial columns of the spinal cord might prove of value to sufferers from spastic paralysis who retain considerable voluntary power, the utilization of which is apparently greatly handicapped by the presence of severe spasticity. The most typical examples of such a condition are the children who suffer from congenital spastic paraplegia or quadriplegia. Many of these children retain a surprising amount of power in the muscles involved, but its full utilization is prevented by overwhelming spasticity, which holds the legs rigidly extended and crossed in the "scissors" position characteristic of this disease.

Numerous attempts have been directed toward alleviation of this condition. Various peripheral nerves have been partially or completely severed. This, of course, results in some reduction of spasticity, but because it also causes complete paralysis and atrophy of the muscle bundles thus rendered flaccid, the procedure defeats its own end. The posterior roots of the spinal nerves have been severed. This procedure rests on sound physiologic principles so far as reduction of the spasticity is concerned, but because it renders the extremities anesthetic for all forms of sensation, both superficial and deep, the operation too greatly impairs the function of an extremity, the coordinated activity of which originally was poor. Other procedures, poorly grounded on physiologic principles or resting on the quicksand of unestablished theory, have also been tried, only to be discarded. They need not concern one here.

METHODS

Shortly after publication of the work of Fulton, Liddell and Rioch, as a test of the adaptability of the procedure under consideration (section of the anteromedial columns of the spinal cord) to treatment of the spastic paralyses, 3 children were chosen. All were practically helpless; all exhibited severe spasticity with more or less voluntary power; all were considerably below the average intellectual level. The pitfalls of depending on purely clinical examinations and observations for interpretation of the results of the procedure were obvious, and means of graphic measurement of the spasticity were sought. (Ulti-

mately, the clinical and laboratory observations proved to be in perfect agreement, but that could not be foreseen.)

Since any attempt at isometric myographic study of individual muscles or groups of muscles is impossible and dangerous, some form of measurement of the resistance of the extremity to passive movement must suffice. Investigation revealed that apparatus based on three sets of principles had been devised. There was that in which the force remained constant and the rate at which the muscle lengthened was measured. There was that in which the rate remained constant and the force was measured. There was a third, designed by Schaltenbrand,[3] in which there were no constants. The knee, for example, could be flexed much as one would flex it in examining a patient. The apparatus recorded graphically the degree of flexion, the rapidity with which the limb was flexed and the resistance offered to this movement. This seemed the most appropriate means of examining the spasticity seen in these patients. True, there were certain handicaps to be met, if possible. A priori, the principal difficulties seemed to be the interference of possible voluntary movements by the patient and the factor of permanent contracture and fibrosis present in the muscles and about the joints of all these patients. Fortunately, the voluntary movements proved to be of little concern. The results of any given examination could be, and were, duplicated again and again in repeated examinations on the same or other days. It was obvious that voluntary innervation, an inconstant factor, did not enter into the measurements. The factor of contracture and fibrosis was even more certainly evaluated. In case 1, the one most thoroughly studied, a spinal anesthetic was given, abolishing all voluntary and reflex muscular activity. The little remaining resistance to passive movement, due to the permanent structural changes in the muscles and joints, lacked the lengthening reaction characteristic of decerebrate rigidity; it is clearly seen in all tracings. The 3 patients who submitted to this operation and the results of the procedure are described here.

REPORT OF CASES

CASE 1.—*A youth aged 16. Congenital spastic paraplegia; mental retardation. Section of the left anterior column of the spinal cord; temporary reduction in spasticity of the left leg; return soon to the preoperative state.*

History.—J. G. was born on May 7, 1916, after a pregnancy of seven and one-half months. The labor of three hours and the delivery were said to have been normal. There was no cyanosis or respiratory difficulty. When the child was 9 months of age, the parents noticed that he was not developing properly. He was observed at another hospital, where a diagnosis of malnutrition was made. The first tooth erupted at the age of 15 months. He began to talk at the age of 20 months. When he was 2 years of age a diagnosis of spastic paraplegia was made. At the age of 3½ a series of tenotomies were performed on the flexor muscles of the knees and on the achilles tendons. A few months later the child first began to stand and walk, with aid. During the subsequent years he was not able to walk more than a few steps without crutches.

3. Schaltenbrand, G.: Messung des Dehnungswiderstandes am menschlichen Muskel bei Gesunden, Spastikern und Parkinsonismusfällen, Deutsche Ztschr. f. Nervenh. **109**:231-251, 1929.

In spite of special instruction, the child did not progress beyond the first grade in school. His intelligence quotient was recorded as 78 at the age of 7, as 73 at the age of 8 and as 68 at the age of 16.

The patient was first seen at the University of Chicago Clinics, in the orthopedic department, on June 9, 1931, when 15 years of age. He had had attacks of pneumonia at the age of 6 weeks, 2 years and 15 years, chickenpox, at the age of 4 and measles at the age of 9. Tonsillectomy was performed at the age of 4, and mastoidectomy, at the age of 6.

The father and mother were living and well. There had been 6 pregnancies; the patient was born of the second. The first child was born dead, as craniotomy

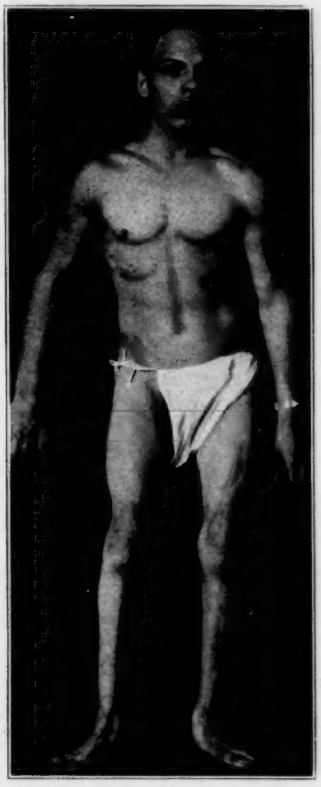

Fig. 1 (case 1).—Photograph of a patient with congenital spastic paraplegia.

was necessary in order to deliver the fetus. One child died of diphtheria. Three other children were living and well.

Examination (Feb. 22, 1932).—In spite of the patient's backwardness in school and mental deficiency, as revealed by the intelligence quotient, he talked well. He was much interested in professional baseball. He knew the names of the various players and the standing of the various teams in the major leagues. He also could recognize and name practically all makes of motor cars at a considerable distance. He lisped.

Above the waist the boy was extremely muscular, well developed and well nourished (fig. 1). General physical examination revealed no abnormalities, except for the lower extremities, to be described later.

Neurologic Examination.—The pupils were normal in all respects. There was slight limitation of external rotation of both eyes. There were coarse, slow nystagmus on looking to the right and rapid, fine nystagmus on looking to the left. There were also coarse vertical nystagmus of the right eye and fine, "jelly" nystagmus of the right eye on central fixation. The cranial nerves were otherwise normal.

The patient was left handed. Strength in the upper extremities was good. Coordination in these extremities was excellent. The patient was able to sit from a supine position without the aid of the arms. However, as he sat the vertebral column was arched, owing apparently to weakness of the musculature of the lower part of the back. The reflexes in the upper extremities were active and equal. The abdominal musculature tended to be rigid. All the abdominal reflexes were present.

There was marked weakness in the lower extremities. The degrees of strength of the various muscle groups are listed in tabular form, the following descriptive adjectives being used: strong (assumed normal strength), moderately strong, moderate, weak, very weak and strengthless.

	Right	*Left*
Hip		
Abduction	Strengthless	Strengthless
Adduction	Strong	Strong
Flexion	Strengthless	Very weak
Extension	Moderate	Moderate
Knee		
Flexion	Moderate	Moderate
Extension	Moderately strong	Moderately strong
Ankle		
Flexion	Weak	Weak
Extension	Weak	Weak

Toes

Practically no voluntary movement except slight plantar flexion was possible. Most attempts at voluntary movement of the feet or toes evoked coarse involuntary clonus at the ankles and of the toes.

The knee jerks were markedly hyperactive. The ankle jerks could barely be obtained (probably because of the tenotomies). Sustained clonus could be elicited at the patellas and the ankles. Babinski's sign could not be elicited. Neither the presence nor the absence of fanning of the toes was recorded.

There was marked spasticity of all extensor muscles in the lower extremities, more in the left. The calves were hard and prominent.

Passive movement of all joints was possible within normal limits.

The patient was able to stand unaided for a short time. The knees were slightly flexed, the right more than the left. He was able to walk only when aided. The weight was borne on the toes and balls of the feet, the heels being raised from the floor.

Diagnosis.—A diagnosis of congenital spastic paraplegia with mental retardation was made.

Operation.—On March 31, with the patient under ether anesthesia, laminectomy of the third, fourth and fifth thoracic vertebrae was done. The spinal cord appeared to be normal. The cord was rotated from the left side until the anterior midline of the cord was visible. A small curved knife was inserted into the substance of

the spinal cord just to the left of the midline and the anterior spinal vessels, at the level of the fifth anterior thoracic spinal root. The entire anterior column of the spinal cord was then cut across, the incision extending lateral to a point just beyond the anterior root (fig. 2).

Postoperative Course.—Two hours after the operation the right leg was extremely spastic, but the spasticity was much less marked on the left side, although the reverse had been true before operation. Three and one-half hours later the same condition obtained, at which time the patient seemed fully conscious.

Twenty-one hours after the operation, however, the left leg was much more spastic than the right, and voluntary movements, such as they were, were more readily executed on the right side.

On the second postoperative day sensory examination (which had not been made before) revealed complete analgesia and thermal anesthesia on the right side of the body, extending up to a point a short distance below the nipple.

During the next several days voluntary movement in the legs returned to the preoperative state.

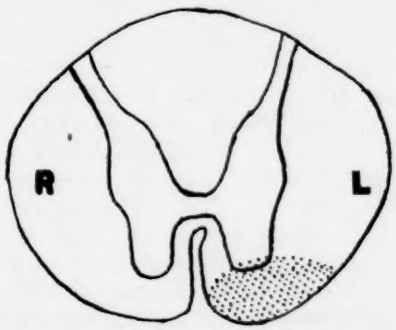

Fig. 2 (case 1).—Diagrammatic sketch of the destructive lesion in the left anterior column of the spinal cord.

On April 8 (the eighth postoperative day) spasticity in the two legs was judged to be equal. Loss of pain and thermal sensibility continued unchanged.

On April 12 spasticity was tested with the patient lying on his back and on the right and left sides. Alteration in position of the body caused no change in the spasticity, which was greatest in the left leg.

The patient was discharged on April 28, at which time, except for the alterations in sensation previously noted, neurologic examination revealed the same findings as before operation.

The patient was readmitted for examination on May 25 and was discharged on June 3. Examination revealed no change in his condition.

The patient was again in the hospital from November 26 to December 4. There was no change in his condition except that the loss of pain and thermal sensibility on the right side was no longer complete, although it extended over the same area as before.

During hospitalization from December 20 to December 22 no change was revealed.

The patient was again admitted on Feb. 6, 1933, and was discharged on February 17. The condition was unchanged.

The patient was followed in the outpatient department at frequent intervals until Sept. 18, 1934. At no time was any change in his condition detected.

Myographic Studies.—For the sake of brevity, only the measurements of the resistance encountered in flexing the leg from a straight position (0 degrees) to one in which the leg was at a right angle to the thigh (90 degrees of flexion) and the intensity of the knee jerks with the leg flexed at varying angles are recorded in this report. Numerous measurements of this sort and many others were made prior to operation. The results were markedly similar. Typical tracings are shown. In obtaining these tracings, two springs were used, one stronger than the other. Although the tracings made with the two springs are similar, representative tracings made with each are reproduced because after the operation the two springs were used at different times.

In both the right and the left leg (figs. 3 *A* and *A'*, and 4 *A*, *A'*, and *B'* and *C'*), rapid flexion of the leg to a right angle with the thigh met with considerable resistance, which developed rapidly and subsided somewhat more slowly (the lengthening reaction) to a more or less constant level of tension, which comparison with figures 3 *B* and *B'* and 4 *B* and *D'* shows to be due largely to contracture and fibrosis. The tracings shown in these figures (3 *B* and *B'* and 4 *B* and *D'*) were obtained with all the voluntary and reflex activity abolished by spinal anesthesia.

The knee jerks elicited in both the right and the left leg were also surprisingly constant (figs. 5 *A* and *A'* and 6 *A* and *A'*). The intensity of the responses, elicited with the usual rubber hammer, increased with increasing flexion of the leg up to about 70 or 80 degrees; beyond that point, i. e., at 80 or 90 degrees of flexion, the intensity remained the same or was decreased (fig. 5 *A'*). With the patient under spinal anesthesia (figs. 5 *B'* and 6 *B*), no knee jerks could be elicited.

After section of the left anterior column of the spinal cord, definite changes in the resistance of the musculature of *both* lower extremities to passive flexion of the legs occurred. No definite difference in the two extremities was detected by the time that myographic studies were undertaken, six days after the operation, although a difference between the two sides had been observed clinically immediately after the operation, as previously noted. Six days after the operation the tracings (figs. 3 *C* and *C'* and 4 *E'*) revealed no more resistance to passive flexion, stretch of the extensor muscles, than was present when the patient was under spinal anesthesia. A similar tracing was obtained from the left leg eight days after operation. This tracing indicated marked diminution or absence of the stretch reflex in the quadriceps extensor muscles. At the same time, strong voluntary movements were present in the right leg (fig. 4 *F'*), but were practically absent in the left. By the eighth postoperative day a definite stretch reflex was present in the right leg (fig. 4 *F'*) but not in the left. On the twelfth day a definite stretch reflex could be elicited on the left side as well (fig. 3 *E'*), but although it was of an intensity comparable with, or greater than, that before operation, it disappeared on repeated testing (figs. 3 *E'* and 4 *F'*). On the fifteenth postoperative day the condition was again similar to that six days after operation (fig. 3 *F'*). By the twenty-first day voluntary power was more consistently elicited in both legs. This recovery progressed, until about two months after operation the resistance to passive flexion had recovered to the preoperative level (figs. 3 *D* and 4 *C*). The intensity of the response was noted to diminish with repeated testing (fig. 3 *D*), but this was not essentially different from what had been observed before the operation (fig. 3 *A'*). Examination about eight months after operation revealed a state (fig. 3 *E* and 4 *D* and *E*) similar to that present before operation

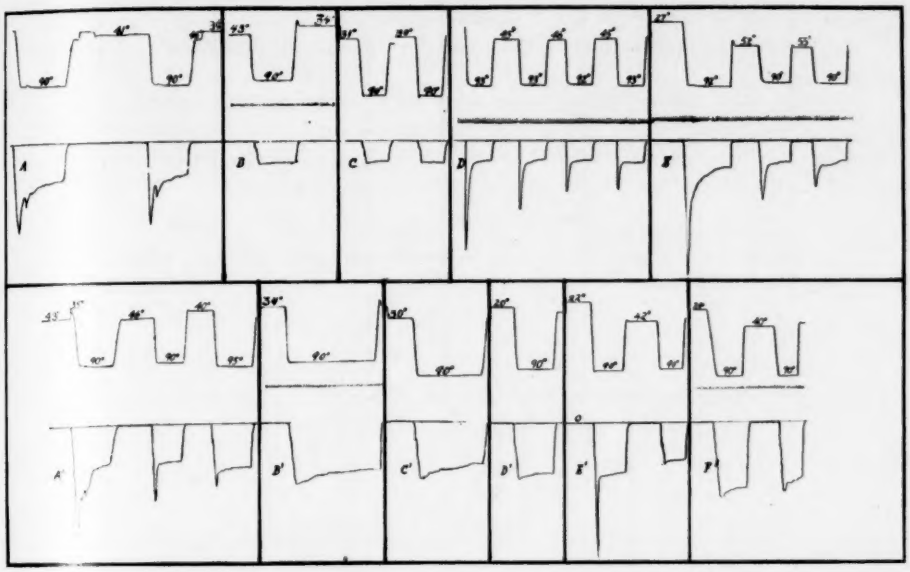

Fig. 3 (case 1).—Tracings for the left leg, showing resistance to flexing the leg to a right angle at the knee.

Of the tracings in this figure and in the accompanying figures, the upper indicates the degree of angulation of the leg on the thigh. Zero degrees (*0*) indicates that the leg is straight; 90 degrees (*90*), that it is flexed to a right angle at the knee. Movement of the leg as indicated in this tracing is always passive; no active voluntary movement is shown except in 1 instance (fig. 4 *F'*). The lower tracing indicates resistance to passive movement. Movement of the tracing downward, away from the base line, indicates increasing resistance. In case 1 resistance was measured by two coil springs, one stronger than the other. The upper tracings in figs. 3, 4, 5 and 6 were obtained with the stronger spring; the lower tracings in the same figures, with the weaker spring. The speed of the drum in all but 2 tracings (fig. 6 *A* and *C'*) was the same; where indicated, it is shown in seconds. In figure 6 *A* and in the latter part of 6 *C'* the drum moved more rapidly.

Tracings *A* to *E* were obtained with the strong spring. *A* was taken on March 28, 1932, before operation, and *B*, on March 16, before operation, with the patient under spinal anesthesia. At the time this tracing was made analgesia extended up to the fifth thoracic dermatome, and anesthesia, up to the eleventh thoracic dermatome. *C* was taken on April 6, six days after section of the left anterior column of the spinal cord; *D* on June 1, two months after the operation, and *E* on December 2, eight months after the operation.

Tracings *A'* to *F'* were taken with the weak spring. *A'* was taken on March 29, before operation, and *B'*, on March 16, before operation, with the patient under spinal anesthesia. At the time this tracing was made examination revealed analgesia up to the fifth and anesthesia up to the eleventh thoracic dermatome. *C'* was taken on April 6, six days after section of the left anterior column of the spinal cord; *D'*, on April 8; *E'*, on April 12, and *F'*, on April 15.

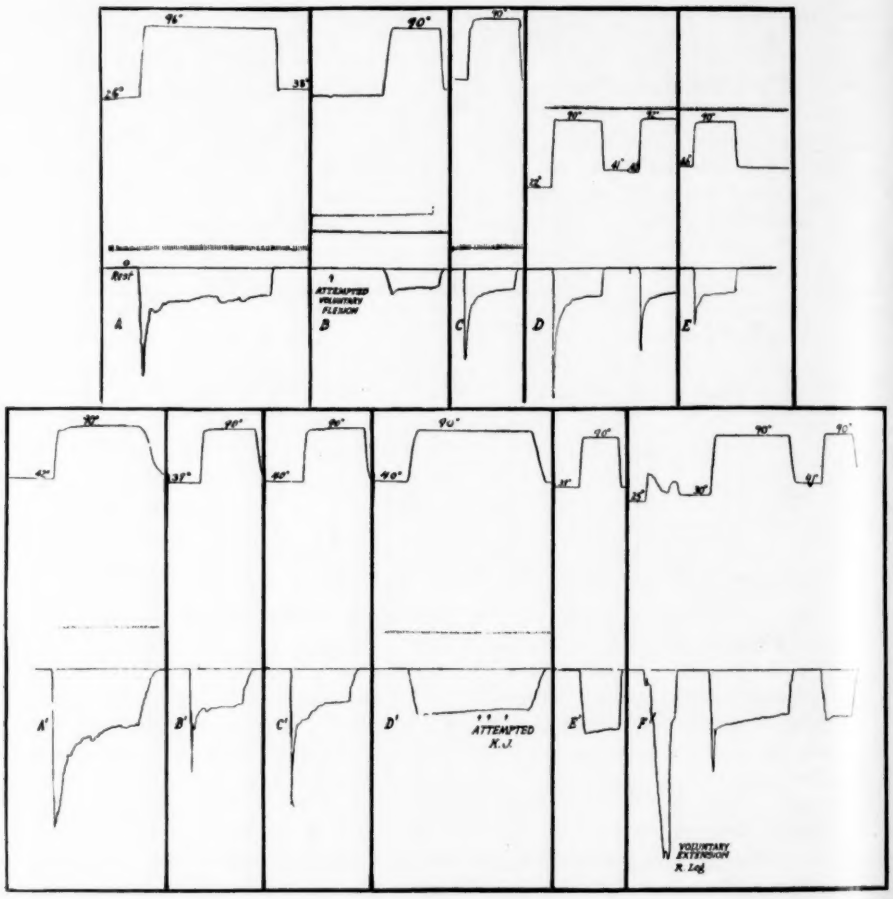

Fig. 4 (case 1).—Tracings for the right leg, showing resistance to flexing the leg to a right angle. Tracings *A* to *E* were taken with the strong spring. *A* was taken on March 3, before operation, and *B*, on March 16, before operation, with the patient under spinal anesthesia. At this time anesthesia extended up to the twelfth thoracic dermatome. All power of voluntary flexion was gone. *C* was taken on May 26, almost two months after the operation, and *D* and *E*, on December 21, eight and a half months after operation. The two tracings shown in *D* are consecutive.

Tracings *A'* to *F'* were taken with the weak spring. *A'* was taken on March 14, before operation; *B'* and *C'*, on March 25, before operation, and *D'*, on March 16, with the patient under spinal anesthesia. There was anesthesia up to the third lumbar dermatome. No knee jerks could be elicited. *E'* was taken on April 6, six days after operation; and *F'*, on April 8, eight days after operation. The first tracing (*F'*) shows the excellent strength in voluntary extension of the leg.

so far as the intensity of the stretch reflex was concerned. In one detail, however, the tracings differed strikingly: Whereas before operation the tension developed by stretching the extensor muscles declined gradually and jerkily, it now declined rapidly and smoothly.

In the tracings of knee jerks on the right side (fig. 6) practically no difference is shown between those taken before and those taken after operation, even on the eighth postoperative day (fig. 6 *B'*). On the left side, however, definite reduction in the intensity of the jerks was noted on the sixth and eighth postoperative

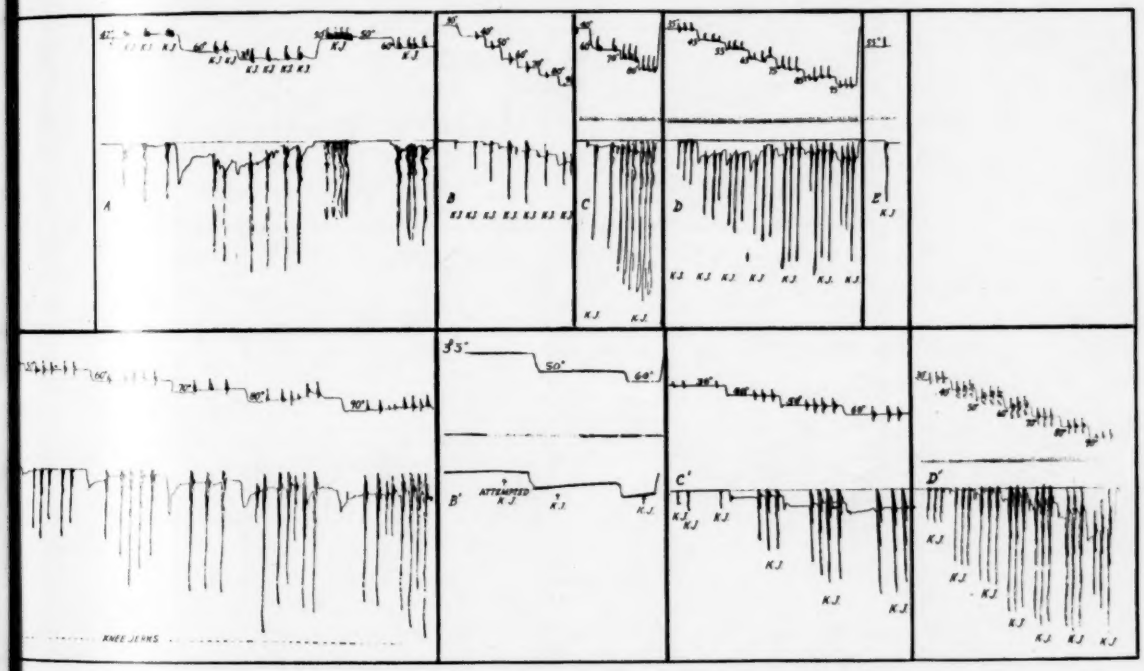

Fig. 5 (case 1).—Tracings for the left leg, showing the intensity of the knee jerk as obtained with the leg in various degrees of flexion. Tracings *A* to *E* were obtained with the strong spring. *A*, March 29, before operation. Knee jerks were elicited with the leg flexed 47, 60, 70, 50 and 60 degrees. *B*, April 8, eight days after operation. Knee jerks were elicited with the leg flexed 30, 40, 50, 60, 70, 80 and 90 degrees. *C*, May 26, fifty-six days after operation. Knee jerks were elicited with the leg flexed 60, 70 and 80 degrees. *D*, June 1, two months after operation. Knee jerks were elicited with the leg flexed 35, 45, 55, 65, 75, 85 and 95 degrees. *E*, December 2, eight months after operation. The knee jerk was elicited with the leg flexed 55 degrees.

Tracings *A'* to *D'* were obtained with the weak spring. *A'*, March 28, before operation. Knee jerks were elicited with the leg flexed 40, 50, 60, 70, 80 and 90 degrees. *B'*, March 16, before operation, with the patient under spinal anesthesia. Analgesia extended up to the sixth thoracic dermatome, and anesthesia up to the third lumbar dermatome. Arrows indicate points at which it was attempted to elicit knee jerks, with the leg flexed at 33, 50 and 60 degrees. *C'*, April 6, six days after the operation. Knee jerks were elicited with the leg flexed 30, 40, 50 and 60 degrees. *D'*, April 19, nineteen days after operation. The leg was flexed 30, 40, 50, 60, 70, 80 and 90 degrees.

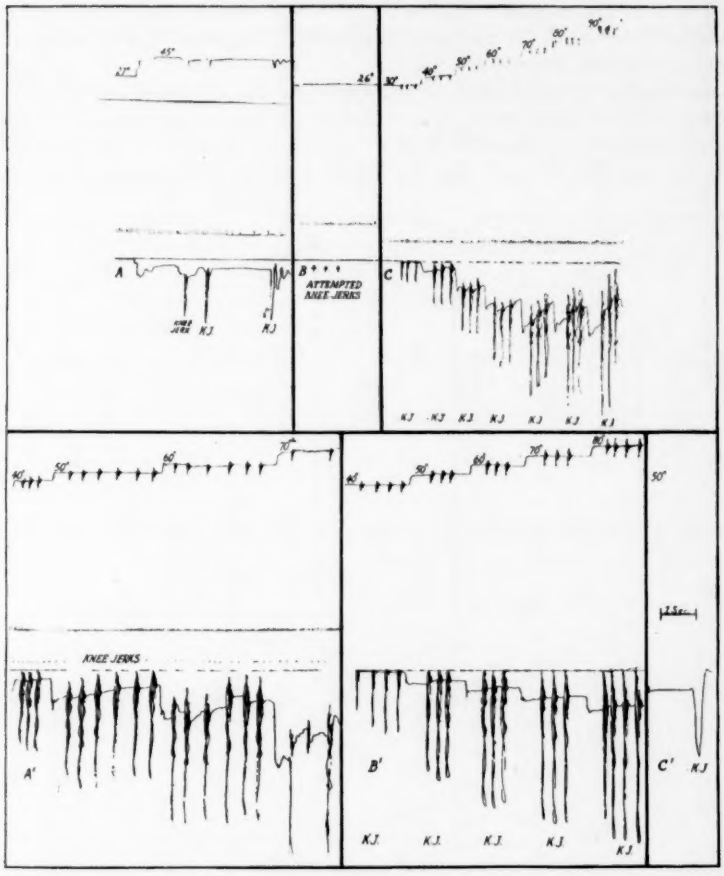

Fig. 6 (case 1).—Tracings for the right leg, showing intensity of knee jerks elicited with the leg in various positions. Tracings *A* to *C* were obtained with the strong spring. *A*, Feb. 23, before operation. Knee jerks were elicited with the leg flexed 45 degrees. The last tracing was taken with the drum moving more rapidly. *B*, March 16, before operation, with the patient under spinal anesthesia. Analgesia extended to the eleventh thoracic dermatome, and anesthesia, to the third lumbar dermatome. An attempt was made to elicit knee jerks with the leg flexed 26 degrees. *C*, November 30, eight months after operation. Knee jerks were elicited with the leg flexed 30, 40, 50, 60, 70, 80 and 90 degrees.

Tracings *A'* to *C'* were obtained with the weak spring. *A'*, March 14, before operation. Knee jerks were elicited with the leg flexed 40, 50, 60 and 70 degrees. An attempt to elicit knee jerks with the patient under spinal anesthesia is shown in figure 4 *D'*. *B'*, April 8, eight days after operation. Knee jerks were elicited with the leg flexed 40, 50, 60, 70 and 80 degrees. *C'*, April 12, twelve days after operation. A knee jerk was elicited with the leg flexed 50 degrees. The drum was moving much faster than in *A'* and *B'*.

days (fig. 5 *B* and *C'*). Within nineteen days after the operation the jerks returned to their preoperative state (fig. 5 *D'*) and remained so (fig. 5 *C*, *D* and *E*). Unfortunately, this method of studying reflex muscular activity is too crude to permit of accurate observations concerning the duration of the knee jerks. Insufficient observations were made regarding the flexor defense reflexes.

In the light of this disappointing experience, it was thought that the incision into the substance of the spinal cord possibly had not involved sufficiently the medial portions of the anterior columns, a necessity which Fulton, Liddell and Rioch had stressed. A different surgical procedure was therefore determined on. It was decided to ligate the anteromedial column and the adjacent anterior spinal artery with a strong braided silk ligature rather than to interrupt the fibers by cutting them. By extension of the ligation to involve the anterior spinal artery and some tissue on the other side, destruction of the most medial part of the anterior column seemed assured. Naturally there was hesitancy about ligating the anterior spinal artery, even at the level of the fourth thoracic vertebra, where it is small and probably relatively insignificant. Because of the potential dangers in this connection, a case in which the prognosis was particularly hopeless was chosen for this operation.

CASE 2.—*A girl aged 10 years. Congenital spastic quadriplegia and idiocy. Ligation of the anterormedial columns of the spinal cord; no reduction in spasticity.*

History.—L. V., a Jewish girl, was born prematurely on Sept. 10, 1922, in the seventh month of pregnancy. Her weight at birth was 4½ pounds (2,041 Gm.). She was cyanotic at birth—a "blue baby." Labor was short; no instruments were used. There was difficulty in breathing, and the child was kept under an oxygen tent for from two to four weeks after birth. It was said that she did not cry for over a month after birth. Shortly after birth she began to have numerous generalized convulsions, as many as five a day. These continued for six months, when they ceased and did not recur. After the first three months of life, breast feeding was supplanted by artificial feeding. The first tooth appeared at the age of 1 year. The child never walked. At 4 years of age she began to talk, but talking did not progress beyond a few words and phrases, which were often irrelevant and spoken in parrot fashion. A short time after birth it was noted that she had severe internal strabismus.

The child had measles at the age of 5 years. An operation for lengthening the tendo achillis was done elsewhere, prior to the age of 10.

The father and mother, aged 47, were well. There were 3 sisters, 2 of whom were, respectively, 9 and 15 years older than the patient. They were all well. The sister 2 years older than the patient was also born prematurely, in the seventh month of pregnancy. One other pregnancy, the third, terminated in the seventh month, the child dying at birth. There had also been 4 miscarriages, 1 at five months, 2 at three months and 1 at six weeks. The relation of these pregnancies to the others is unknown. Three paternal aunts were stated to have died of tuberculosis. The Wassermann reactions for both parents were negative.

Examination (April 26, 1932).—The head appeared abnormally small for a child of 10 years. There was a marked growth of hair extending well over the forehead (fig. 7). The eyebrows met in the midline. The mouth was large,

and the teeth were widely spaced. The tonsils were large. There was generalized enlargement of the cervical lymph glands. The heart and lungs were normal to auscultation and percussion. The blood pressure was 120 systolic and 70 diastolic. Examination of the abdomen was difficult because of muscular spasm. No masses were palpated. There was definite, though mild, scoliosis.

Neurologic Examination.—Mentally the child was severely retarded. There was little evidence that she was at all cognizant of her environment. She laughed frequently, at times almost continuously. She was able to enunciate a few words. These she repeated frequently and entirely without relevance to what was said

Fig. 7 (case 2).—Patient with congenital spastic quadriplegia.

to her or went on about her. Speech consisted almost exclusively of such statements as the following: "She wants to go to beach"; "Want to go in elevator"; "She is going to have mashed potatoes and gravy"; "She is going to have a sand bath"; "Yes"; "Waa." She was incontinent of both urine and feces.

Cranial Nerves: The patient appeared to see light and objects with both eyes. The optic disks and fundi were normal. The pupils were round and equal and reacted normally to light. There was alternating internal strabismus. Ocular movements were full in all directions except for upward conjugate movement, which appeared to be defective. The corneal reflexes were active. There was a definite response to pinprick over the entire face. There was no weakness of the muscles of mastication. No facial weakness was present. The child seemed

to hear with both ears. The palate moved in the midline when stimulated. No difficulty in swallowing was apparent. There was no wasting or weakness of the sternocleidomastoid or trapezius muscles. The tongue was protruded in the midline, with no atrophy or fibrillation.

Reflexes: The tendon reflexes in the upper extremities were present and equal on the two sides; they were not hyperactive. The abdominal reflexes were absent. The knee jerks were hyperactive. Babinski's sign was not elicited.

Sensation: Perception of pinprick seemed intact everywhere. Other forms of sensation could not be tested accurately.

Motor Function: There was no limitation of movement of the neck. The patient was unable to lift her head. It was impossible to test voluntary power. The patient lay in bed with both arms flexed at the elbows, lying across the abdomen or chest, with the hands meeting or crossing in the midline. The fingers were partially flexed. She was able to move the arms and to extend the elbows to about 120 degrees. She grasped objects with reasonable power, but all such movements were slow and poorly coordinated. There was definite resistance to passive stretching of the flexor muscles of the wrist and elbow, but not of the extensor muscles. The abdominal musculature was rigid on palpation. There was no evidence of any voluntary movement in the lower extremities. The patient was unable to stand or walk. When the patient was held in midair by the examiner, the thighs were partially flexed on the abdomen (fig. 7). The knees were semiflexed and the feet either dorsiflexed or held at a right angle to the leg. There was a definite adductor spasm in both thighs. There was considerable resistance to passive stretching of both the extensor and the flexor muscles of the knees. Plantar flexion of the feet beyond 90 degrees was not possible. Nociceptive stimuli to the lower extremities elicited marked defense, withdrawal or flexor responses bilaterally.

Laboratory Examination.—Wassermann and Kahn tests of the blood gave negative results. A blood count revealed 8,000 leukocytes, 4,800,000 erythrocytes and 90 per cent hemoglobin. Urinalysis revealed nothing abnormal.

Diagnosis.—The diagnosis was congenital spastic quadriplegia and imbecility.

Operation.—On July 21, with the patient under ether anesthesia, the spines and laminas of the third, fourth and fifth thoracic vertebrae were removed. The spinal cord appeared to be normal. By traction on the dentate ligaments, the cord was rotated until the anterior midline was visible. A small curved aneurysm needle threaded with a long silk thread was inserted 1 or 2 mm. to the left of the anterior spinal artery, pushed across the midline and brought out 3 or 4 mm. to the right of the artery. The needle was removed and the thread tied tightly, the anteromedial fibers of the spinal cord being compressed or cut and the anterior spinal artery ligated. About 1 cm. below this point the same procedure was again carried out, except that the needle was inserted from right to left in order that the lesion in the two anterior columns might be as symmetric as possible (fig. 8).

Postoperative Course.—On the afternoon of the day of operation there seemed to be less resistance to passive movement in the lower extremities than previously. It was soon obvious, however, that the patient's condition was not altered, except that the flexor defense reflexes were thought to be somewhat more active than before operation. However, as they were always very active, this was difficult to judge. The patient was repeatedly and carefully examined for almost two months after operation. She was discharged on Septembr 11. Occasional observation in the outpatient department since have revealed no apparent change in the condition of the lower extremities.

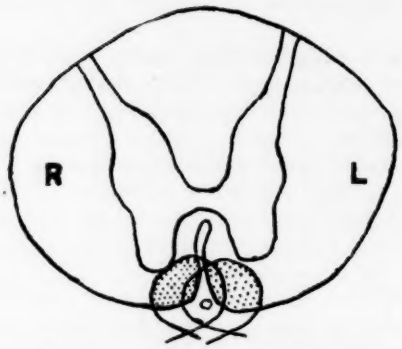

Fig. 8 (case 2).—Schematic drawing of lesions made in the anteromedial columns of the spinal cord by ligation.

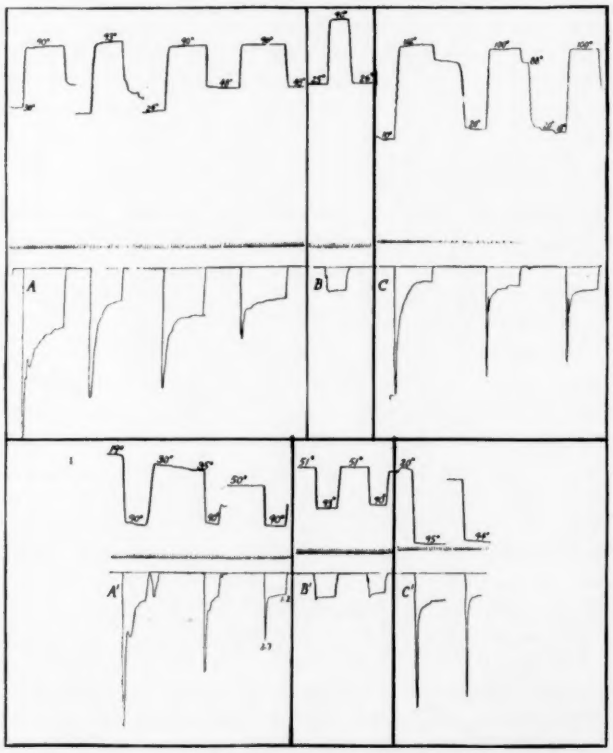

Fig. 9 (case 2).—*A* to *C*, tracings for the right leg, showing resistance to flexing the leg to a right angle. *A*, July 5, before operation. The four tracings were not taken consecutively. *B*, May 24, before operation, with the patient under anesthesia induced with nitrogen monoxide. *C*, August 3, thirteen days after operation. The three tracings were taken consecutively.

A' to *C'*, tracings for the left leg. *A'*, May 16, before operation. The first two tracings were taken consecutively; the third did not follow the second immediately. *B'*, May 24, with the patient under anesthesia induced with nitrogen monoxide. *C'*, September 2, six weeks after the operation. The tracings were not taken consecutively.

Myographic Studies.—Tracings made before operation (figs. 9 *A* and *A'*) indicated a condition comparable with that in case 1. It was again noted that subsidence of the tension produced by flexing the leg was gradual and jerky. There was usually a "hump" in this part of the tracing. The tracings shown in figure 9 *A* and *A'* have been chosen to show the limits of variability of the response to flexing the leg.

With the patient anesthetized with nitrogen monoxide the stretch reflex disappeared (fig. 9 *B* and *B'*), as it did in the first patient when under the spinal anesthesia. The remaining resistance to passive flexion of the leg was due to fibrosis of the soft tissues in and about the muscles and knee joints.

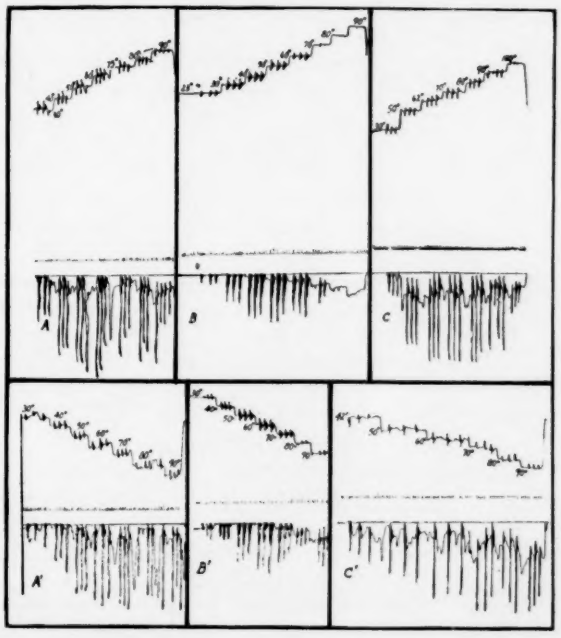

Fig. 10 (case 2).—*A* to *C*, tracings for the right leg. *A*, May 9, before operation. Knee jerks were elicited with the leg flexed 30, 40, 50, 60, 70, 80 and 90 degrees. *B*, May 24, with the patient under anesthesia induced with nitrogen monoxide. Knee jerks were elicited with the leg flexed 23, 30, 40, 50, 60, 80 and 90 degrees. *C*, September 7, seven weeks after operation. Knee jerks were elicited with the leg flexed 30, 50, 62, 70, 80, 90 and 100 degrees.

A' to *C'*, tracings for the left leg. *A'*, May 16, before operation. Knee jerks were elicited with the leg flexed 30, 40, 50, 60, 70, 80 and 90 degrees. *B'*, May 24, with the patient under anesthesia induced with nitrogen monoxide. Knee jerks were elicited with the leg flexed 30, 40, 50, 60, 70, 80 and 90 degrees. *C'*, September 8, seven weeks after operation. Knee jerks were elicited with the leg flexed 42, 50, 60, 70, 80 and 90 degrees.

Unfortunately, in this case graphic studies of the resistance of the extensor musculature of the legs to passive stretching were not made until two weeks after the operation. At that time the amount of resistance to passive flexion

of the legs was almost as great as before operation (fig. 9 *C*). A month later (fig. 9 *C'*) the resistance was perhaps a little greater, but the condition was essentially unchanged.

Again, as in case 1, it is noteworthy that after section of the anteromedial columns of the spinal cord the tension developed by flexing the leg subsided more rapidly and smoothly than before, and there was usually no secondary "hump."

The knee jerks elicited both before and after operation (fig. 10 *A, C, A'* and *C'*) were essentially the same. With anesthesia induced with nitrogen monoxide, the jerks were not abolished as they were with spinal anesthesia, but were markedly reduced in intensity.

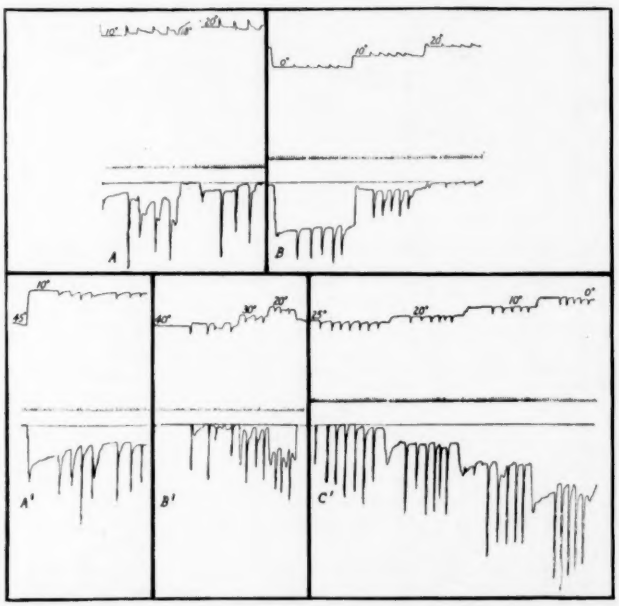

Fig. 11 (case 2).—*A* and *B*, tracings for the right leg. Flexor defense reflexes were elicited by stimulating the sole of the right foot (*A*) and the left foot (*B*) with a pin. The records are therefore not comparable. *A*, May 9, before operation. The leg was flexed 10 and 20 degrees. *B*, September 2, six weeks after operation. Tracings were taken with the leg in full extension (*0*) and flexed 10 and 20 degrees.

A', *B'* and *C'*, tracings for the left leg. Flexor defense reflexes were elicited by stroking the sole of the left foot only. *A'*, May 9, before operation. The leg was flexed 10 degrees. *B'*, May 16, before operation. The leg was flexed 40, 30 to 20 degrees. *C'*, September 1, six weeks after operation. Tracings were taken with the leg flexed 25, 20 and 10 degrees and in full extension (*0*).

Clinically, it was thought that the flexor defense reflexes, which were very active before operation, were even more active afterward. Unfortunately, a graphic study of this point sufficient to confirm this impression was not made. However, the tracings available lend support to this view. As shown in figure 11 *A'* and *B'*, the flexor responses to stimulating the sole of the foot with a

pin were definitely less intense than those obtained after operation, as shown in figure 11 *C'*. Observations for the right leg (fig. 11 *A* and *B*) were not comparable.

No untoward effects from ligating the anterior spinal artery having been seen in case 2, it was decided to repeat this procedure in case 3 and to extend the lesion somewhat more laterally. The patient utilized in this instance suffered from incapacitating spastic paraplegia, but the intellectual deficit was not as great as that in case 2.

CASE 3.—*A girl aged 11½ years. Congenital spastic paraplegia and mental retardation. Ligation of the right anterior column of the spinal cord and the anterior spinal artery. Evidence of complete transverse interruption of the spinal cord.*

History.—D. C. was born on Jan. 20, 1921, during the seventh month of pregnancy. The mother was in labor for forty-eight hours before the child was delivered, with forceps. At birth the child was cyanotic and was referred to as a "blue baby." Shortly after birth she began to have attacks of screaming at night and convulsions. These occurred from one to three times a week for the first three years of life. They were characterized by frothing at the mouth, cyanosis and generalized tonic and clonic movements.

The child was never able to stand without support or to walk. The legs gradually grew more rigid as she grew older. At the age of 4 years tenotomies were performed at the knees and ankles; although these served to straighten the lower extremities, they did not improve the ability to stand or walk.

It was soon apparent that the child was mentally retarded. In 1932, at the age of 11 years and 4 months, examination with the Stanford revision of the Binet-Simon tests revealed an intelligence quotient of 63 (mental age of 7 years and 2 months). She did not pass beyond the first grade in school.

The child had had whooping cough and measles, without complications.

The parents were living and well. Five brothers and 4 sisters were living and well. Two siblings had died, 1 at 9 days and 1 at 7 months of age. The patient was the fourth child born in this family.

Examination.—General physical examination revealed nothing abnormal except a deformity of the chest commonly referred to as pigeon breast.

Neurologic Examination (May 20, 1932).—The optic disks and fundi were normal. There was bilateral hypermetropia. The pupils were irregular, but reacted normally. There was fine nystagmus on looking to the right. The cranial nerves were otherwise normal.

Sensation was intact. Voluntary movements in the upper extremities were stiffly and poorly performed. The left arm could not be fully extended. The arms were commonly held flexed on the chest. Weakness was greatest in the adductor muscles of the fingers and the flexor and extensor muscles of the wrist. In spite of these disabilities, however, the child was able to feed and at times to dress herself. All tendon reflexes in the upper extremities were hyperactive. There was some spasticity in the muscles, particularly the flexors, which was greatest on the left side. The patient was unable to sit up without the use of the arms. There was no marked rigidity of the abdominal musculature. The abdominal reflexes were active.

She was unable to walk unassisted. When aided, she walked with the knees slightly bent and lifted the feet high in the air. There was a marked "scissors" phenomena (adductor spasm). There was marked resistance to passive stretch-

ing of all muscles in the lower extremities (spasticity). Voluntary movements in the lower extremities were poorly and weakly executed. The toes could not be moved voluntarily. All other movements were possible, though limited.

The knee jerks were extremely hyperactive, and the ankle jerks were moderately so. There were an unsustained patellar, and at times an ankle, clonus on both sides. The Babinski sign was present bilaterally.

Diagnosis.—The diagnosis was cerebral spastic quadriplegia with mental retardation.

Operation.—On August 23 laminectomy of the second, third, fourth and fifth thoracic vertebrae was performed with the patient under ether anesthesia. The spinal cord appeared normal. The cord was rotated from the right side. An aneurysm needle bearing a silk thread was inserted just to the left of the anterior part of the midline and the anterior spinal artery and was brought out at the point of emergence of the right anterior spinal root. The thread was tied, ligating the right anterior column and the anterior spinal vessels at this point. A second ligature was inserted just to the right of the midline and brought out

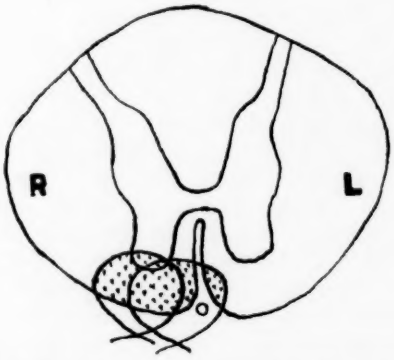

Fig. 12 (case 3).—Schematic drawing showing the lesion made in the right anterior column of the spinal cord.

farther lateral on the right side than the first ligature, thus insuring destruction of the entire right anterior column (fig. 12).

Postoperative Course.—On the first day after operation the left leg was much less spastic than the right. The patient had retention of urine and had to be catheterized. On the following day the temperature rose to 103 F. The legs were relaxed. No voluntary movement was possible. There was total anesthesia up to the sixth thoracic dermatome. Marked flexor defense reflexes were present. The knee jerks were sluggish, and the ankle jerks and the abdominal reflexes were absent. Lumbar puncture revealed incomplete block of the spinal subarachnoid space.

Since it was believed that a hematoma had developed, the wound was reopened. Although the usual small amount of blood was observed in the epidural space, it did not seem sufficient to have caused the symptoms of complete interruption of the spinal cord. Because of a small stitch abscess in the subcutaneous tissues, the dura was not opened. The wound was drained, and it was several weeks before it healed completely.

On September 8 the sensory level was unchanged. Paralysis of the bladder continued. No voluntary power was present in the legs. The lower extremities were flaccid. Flexor defense reflexes were very active. The abdominal reflexes and the knee and ankle jerks were all absent. Plantar stimulation evoked only slight plantar flexion of the great toe.

On September 20, twenty-eight days after the operation, sensory loss was unchanged, and the defense reflexes were very active. Nociceptive stimuli applied to one lower extremity (particularly pinching the tendo achillis) caused flexor withdrawal of that extremity and a strong extensor response in the other leg. The knee jerks were active. The ankle jerks could be readily obtained, but were not as active. The Babinski sign could not be elicited.

The patient's condition did not change subsequently, and she was discharged on November 4.

She was again in the hospital from December 9 to Jan. 18, 1933. There were constipation and almost constant urinary incontinence. A small decubitus ulcer was present in the coccygeal region. There was loss of all sensation up to about the nipple line. No voluntary movement was present. There was marked atrophy of the musculature of the lower extremities. Slight flexor defense reflexes could be elicited. Plantar stimulation evoked slight plantar flexion of all the toes. The tendon reflexes were absent.

The patient was last seen on Nov. 5, 1935, at which time the condition of complete paralysis and anesthesia below the nipples was still present.

COMMENT

The data presented contain one serious defect. It has not been possible to confirm the exact location and extent of the lesion which was made. However, as there does not seem to be any possibility of such confirmation for many years, it was judged advisable to report the findings as they stand.

Superficially, it may appear that the observations made on these patients are at variance with those made by Fulton, Liddell and Rioch [2] on the cat. Careful examination of the two sets of data shows them to be in agreement. The original observations made on the effect of anteromedial chordotomy on decerebrate rigidity in the cat were in acute experiments only. Subsequently, Liddell [4] extended this investigation to chronic experiments, and these will be referred to subsequently. The observations on the effect of unilateral destruction of the vestibular nuclei were, however, made in both acute and "chronic" experiments; i. e., in the "chronic" experiments the vestibular nuclei were destroyed three weeks prior to decerebration of the animals. Even in this short period it was noted that "in all cases the intensity of the symptoms became considerably less marked with time." In these instances, even though the vestibular nuclei had been destroyed on one side, decerebration resulted in "good extensor rigidity" in the ipsilateral

4. Liddell, E. G. T.: The Influence of Experimental Lesions of the Spinal Cord upon the Knee-Jerk, Brain **59**:160-174, 1936.

as well as in the contralateral limbs; the stretch reflex was present on both sides, though on occasion it was less active on the side of operation; the knee jerks were present, though they were of somewhat longer duration and were more readily inhibited in the ipsilateral extremities, and the crossed extensor reflex could be elicited on both sides. This led the authors to conclude that tracts other than the vestibulospinal pathways were concerned, though to a less degree, with the maintenance of decerebrate rigidity. These observations should perhaps have served as a warning that section of the vestibulospinal tract would reduce only temporarily the spasticity in man. However, knowledge that the flaccidity which follows section of the spinal cord in man is more severe and more enduring than that in the cat gave some hope that section of this tract in man would result in more permanent reduction of the spasticity. The fact that such was not the case, together with the observations made in case 3 that a transverse lesion of the spinal cord in a child with spastic paraplegia resulted in flaccidity far more severe and enduring than that which follows section of the vestibulospinal tracts, indicates that other tracts from a supraspinal center or centers are also concerned in the maintenance of the extensor rigidity characteristic of the decerebrate state in the laboratory animal and of spastic paralysis in man.

In 1934, after these observations on patients had been completed, Liddell [5] reported on his studies on the knee jerk, its susceptibility to inhibition and the stretch reflex in chronic spinal preparations (cats), as long as sixty days after section of the spinal cord. He found that the inhibitability of the knee jerk becomes progressively less, until after fifty or sixty days the condition resembles that present in a decerebrate preparation. He stated further:

> Collateral evidence, derived from the degree of muscular extension needed to produce a given background of excitability, suggests restitution of the central excitatory state to almost normal values in the spinal centers.

More recently, Liddell [4] continued the work of Fulton, Liddell and Rioch, making observations on cats as long as a year after anterior chordotomy. However, as the lesions in his preparations were described as being ventrolateral rather than ventromedial, it is questionable whether the observations can be compared with those made here or in the acute experiments on animals.[6]

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5. Liddell, E. G. T.: Spinal Shock and Some Features in Isolation-Alteration of the Spinal Cord in Cats, Brain **57**:386-400, 1934.

6. In a personal communication (March 31, 1937), Dr. Liddell expressed the opinion that in the cat there is considerable "scatter" of the descending pathways concerned with the maintenance of decerebrate rigidity, and that when a certain proportion of these descending paths are sectioned, the alterations characteristic of the "spinal" cat, described by Fulton, Liddell and Rioch, appear.

Unfortunately, it was not possible in the patients in this study to duplicate in their entirety the observations made in the cat. Thus, it was not feasible to determine the duration of the knee jerk with sufficient accuracy to make such an observation of value. Neither was it possible to determine the inhibitability of the knee jerks. However, it was shown that for a short time following section of the anteromedial columns of the spinal cord the intensity of the stretch reflexes and the knee jerk is reduced. In view of the findings in case 1, it may legitimately be asked how much these changes resulted from section of the anteromedial column—the vestibulospinal tract—and how much they were dependent on temporary damage to other tracts in the spinal cord, through edema and interference with the blood supply, and possibly hemorrhage. It will be recalled that in this case, in which section was limited to one side of the spinal cord, the changes which occurred in the ipsilateral lower extremity differed from those in the contralateral extremity only slightly, in that they persisted a few days longer. It is, of course, probable that the greatest damage to the spinal cord outside the area sectioned was to contiguous areas, one of which was the opposite anteromedial column. This may explain the remarkable symmetry present in the changes which followed this operation.

One other point attracts particular attention, as it raises again a point which Buchanan and I have previously discussed.[7] It will be recalled that before operation all the patients showed relatively slow and jerky subsidence of the tension caused by stretching the extensor muscles of the leg. The jerkiness or "hump" is probably comparable to the "hump," or myotatic appendage, seen on the curve of relaxation of the knee jerk in the decerebrate state. It is not present in the spinal preparation. It has previously been stated that the relaxation in tension of the stretch reflex in children with spastic paralysis is the "lengthening reaction." It will be noted that the relaxation occurs while the process of stretching the muscles is still at its height, i. e., while the leg is still flexed at a right angle. Various adherents of the Sherrington school have attributed the lengthening reaction to autogenous inhibition developing from stimulation of sensory end organs in the muscle subjected to this severe tension. Buchanan and I,[7] while not denying the possible existence of autogenous inhibition, pointed out that it is not necessary to call on this theoretic burst of autogenous inhibitory impulses to explain the lengthening reaction. The present observations, however, indicate that after section of the anteromedial columns of the human spinal cord autogenous inhibition probably is

7. Bucy, P. C., and Buchanan, D. N.: Studies in the Human Neuro-Muscular Mechanism: I. The Theory of "Subsidence of Afferent Flow" as an Explanation of the "Lengthening Reaction" and Other Phenomena, Am. J. Physiol. **104:** 95-112, 1933.

responsible for the more rapid relaxation, which is the lengthening reaction, and for the smoothness of this relaxation, i. e., the absence of the hump, or myotatic appendage. This observation confirms that of Fulton, Liddell and Rioch that section of the anteromedial portion of the spinal cord increases the inhibitability of the stretch reflex.

CONCLUSIONS

In 3 patients suffering from congenital spastic paraplegia or quadriplegia, one or both anteromedial columns of the spinal cord were sectioned in the upper thoracic region. No permanent reduction in spasticity, the stretch reflex or the intensity of the knee jerks resulted. For only a few weeks the stretch reflex and the intensity of the knee jerks were reduced. The lengthening reaction which developed relatively slowly and jerkily before operation occurred more rapidly and smoothly afterward. This was interpreted as due to increased inhibitability of the stretch reflex.

In 1 instance the anterior spinal artery was ligated in the upper thoracic region in association with destruction of the anteromedial columns of the spinal cord, with no untoward results. In a second instance, however, this procedure resulted in symptoms of transverse interruption of the spinal cord and complete flaccidity of the previously spastic muscles below that level. This flaccidity, typical of interruption of the spinal cord in man, was far more severe and lasting than that which followed section of the anteromedial columns, the vestibulospinal tracts.

It was thus concluded that although the vestibulospinal tract contributes to maintenance of the extensor rigidity associated with spastic paralysis in man and that its destruction increases the inhibitability of the stretch reflex, there are other pathways arising in supraspinal centers which are also concerned in maintaining this spasticity and which are fully capable of maintaining it at its full intensity, even after section of the anteromedial columns of the spinal cord.

STUDIES IN DISEASES OF MUSCLE

IV. METABOLISM OF CREATINE AND CREATININE IN MUSCULAR WASTING SUBSEQUENT TO DISEASE OF THE NERVOUS SYSTEM

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AND

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Creatinuria and diminished excretion of urinary creatinine are common findings in patients with muscular wasting subsequent to disease of the nervous system. As early as 1909 Levene and Kristeller [1] observed that some patients with muscular involvement of this kind excrete creatine and have a lowered creatinine output. Many investigators have confirmed these findings and have extended the observations to various types of muscular wasting. However, understanding of the mechanism of creatinuria in these conditions is not yet clear. Furthermore, it is not known whether the factors influencing the metabolism of creatine and creatinine associated with muscular wasting subsequent to a lesion of the nervous system are similar to those which determine the excretion of creatine and creatinine in progressive muscular dystrophy (Milhorat and Wolff [2]).

MATERIAL AND METHODS

In the present investigation 17 patients with muscular wasting due to a variety of conditions were studied. The group included patients with Charcot-Marie peroneal muscular atrophy and with muscular involvement subsequent to peripheral neuritis, anterior poliomyelitis, amyotrophic lateral sclerosis and so-called neuronitis.

The methods used in carrying out these investigations were similar to those previously described for a group of patients with progressive muscular dystrophy.[2] The patients were maintained on a diet free from creatine and creatinine for the duration of the studies. The urine was carefully collected in twenty-four hour samples, and the output of preformed creatinine and of creatine was determined daily. After an adequate period of control, a test dose of creatine (1.32 Gm.)

From the New York Hospital; the Department of Medicine, the Cornell University Medical College, and the Russell Sage Institute of Pathology.

1. Levene, P. A., and Kristeller, L.: Factors Regulating the Creatinin Output in Man, Am. J. Physiol. **24**:45, 1909.

2. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: I. Metabolism of Creatine and Creatinine in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **38**:992 (Nov.) 1937.

was given, and the ability of the patient to retain ingested creatine was estimated. The ability to retain exogenous creatine is referred to as the "creatine tolerance" and is expressed as the percentage of ingested creatine retained by the patient. After a second period as a control, the patient was usually given aminoacetic acid, and the effect of the ingested amnioacetic acid on the spontaneous output of creatine and the creatine tolerance was determined. In the earlier reports of this series [3] will be found a more detailed description of the methods and a discussion of the biologic significance of creatine, creatinine and aminoacetic acid.

TABLE 1.—*Effect of Ingested Creatine and Aminoacetic Acid on Excretion of Urinary Creatine and Creatinine in Patients with Muscular Wasting Subsequent to "Progressive Anterior Poliomyelitis"*

Patient	Days in Period	Total Urinary Nitrogen Daily, Gm.	Urinary Creatinine Daily, Gm.	Urinary Creatine Daily, Gm.	Aminoacetic Acid per Day, Gm.	Creatine		Creatinine Index, Mg. of Creatinine per Kg. of Body Weight
						Given, Gm.	Retained, %	
Case 8, H. S., male, age 39, 65 Kg.	3	10.30	0.965	0.005				
	3	9.13	0.838	0.169	..	1.5	56	
	2	8.73	0.873	0				
	5	10.87	0.851	0.122	20	...	..	14.8
	3	11.26	0.876	0.583	20	1.5	0	
	4	12.89	0.970	0.156	20			
Case 9, P. V., male, age 67, 46 Kg.	4	7.34	0.711	0.054				
	2	5.44	0.622	0.206	..	1.32	70	
	1	5.82	0.647	0.095	..	....	..	15.2
	2	6.94	0.795	0.039	20			
	2	8.16	0.648	0.344	20	1.32	40	
Case 10, K. P., female, age 25, 51 Kg.	3	6.37	1.008	0				
	1	6.25	0.900	0.274	..	1.32	73	
	1	6.16	1.000	0				
	2	8.39	1.000	0	20	....	..	19.6
	2	7.26	1.125	0	20	1.32	100	
Case 11, E. F., male, age 52, 66 Kg.	(1935)							
	1	8.90	1.197	0.043				
	1	9.05	1.253	0.200	..	1.32	84	18.4
	(1936)							
	1	6.45	0.720	0.630				
	1	6.33	0.720	1.480	..	1.32	15	10.9
Case 12, A. L., male, age 36, 73 Kg.	1	....	1.845	0				
	1	....	1.772	0.238	..	1.32	76	25.2
Case 13, C. P., male, age 61, 74 Kg.	1	....	1.200	0.103				
	1	....	1.124	0.514	..	1.32	59	16.3

* In this table and in the accompanying tables, the daily creatinine excreted is preformed creatinine.

† In this table and in the accompanying tables, creatine is expressed as creatinine.

OBSERVATIONS

Spontaneous Excretion of Creatine.—Most of the patients excreted only moderate or minimal amounts of urinary creatine (from 0.005 to 0.1 Gm.), even when a considerable degree of muscular disability was present. Even when the degree of muscular disability approached that observed in some persons with progressive muscular dystrophy the elimination of creatine was small. H. S. (table 1), with progressive

3. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: II. Effect of Varying Amounts of Ingested Creatine on Creatine Tolerance in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **39**:37 (Jan.) 1938; footnote 2.

TABLE 2.—*Effect of Ingested Creatine and Aminoacetic Acid on Excretion of Urinary Creatine and Creatinine in Patients with Muscular Wasting Subsequent to Peripheral Neuritis*

Patient	Days in Period	Total Urinary Nitrogen Daily, Gm.	Urinary Creatinine Daily, Gm.	Urinary Creatine Daily, Gm.	Aminoacetic Acid per Day, Gm.	Creatine Given, Gm.	Creatine Retained, %	Creatinine Index, Mg. of Creatinine per Kg. of Body Weight
Case 1, M. S., male, age 48, 58 Kg.	4	6.59	0.992	0.059				
	3	6.69	1.007	0.177	..	1.32	84	
	2	6.63	1.148	0.022				
	7	8.74	1.072	0.025	20			
	2	11.59	1.072	0.013	40	....	..	18.4
	3	13.73	1.271	0.247	40			
	2	13.73	1.219	0.034	..	1.32 daily	84	
Case 2, J. B., male, age 44, 78.2 Kg.	1	8.90	1.475	0.013				
	1	9.25	1.350	0.083	..	1.32	93	18.9
	1	10.59	1.542	0.015				
Case 3, P. L., male, age 24, 53.2 Kg.	1	8.30	1.300	0.022				
	2	8.03	1.340	0.093				
	2	8.14	1.327	0.023	20	1.32	86	24.5
	2	8.49	1.306	0.120	20	1.32	81	
	1	9.08	1.297	0.060				

TABLE 3.—*Effect of Ingested Creatine and Aminoacetic Acid on Excretion of Urinary Creatine and Creatinine in Patients with Muscular Wasting Subsequent to Amyotrophic Lateral Sclerosis*

Patient	Days in Period	Total Urinary Nitrogen Daily, Gm.	Urinary Creatinine Daily, Gm.	Urinary Creatine Daily, Gm.	Aminoacetic Acid per Day, Gm.	Creatine Given, Gm.	Creatine Retained, %	Creatinine Index, Mg. of Creatinine per Kg. of Body Weight
Case 14, A. B., male, age 38, 84.5 Kg.	4	11.37	1.851	0.100				
	1	10.60	1.785	0.225	..	1.32	90	
	5	9.66	1.789	0.100				
	4	12.55	1.831	0.101	20	....	..	21.9
	1	12.53	1.747	0.180	20			
	2	13.30	1.882	0.023	20	1.32	93	
Case 15, E. L., female, age 65, 90.2 Kg.	3	7.09	0.868	0.070				
	1	8.07	1.041	0.418	..	1.32	66	
	3	7.00	0.944	0.088	..	....	..	10.0
	5	10.97	0.995	0.186	20	1.32	42	
	3	9.36	0.912	0.412	20			
Case 16, S. W., female, age 66, 42 Kg.	1	....	0.355	0.333				
	1	....	0.363	1.047	..	1.32	22	8.5
	1	....	0.353	0.399				

TABLE 4.—*Effect of Ingested Creatine and Aminoacetic Acid on Excretion of Urinary Creatine and Creatinine in a Patient with Muscular Wasting Subsequent to Acute "Neuronitis," Presumably Infectious, of Unknown Origin*

Patient	Days in Period	Total Urinary Nitrogen Daily, Gm.	Urinary Creatinine Daily, Gm.	Urinary Creatine Daily, Gm.	Aminoacetic Acid per Day, Gm.	Creatine Given, Gm.	Creatine Retained, %	Creatinine Index, Mg. of Creatinine per Kg. of Body Weight
Case 17, H. P., female, age 28, 40 Kg.	4	4.08	0.231	0.244				
	2	5.76	0.255	0.792	..	1.32	0	5.8
	2	8.14	0.269	0.713	20			
	4	2.75	0.231	0.284				

weakness and wasting of the muscles secondary to chronic anterior poliomyelitis, excreted only negligible amounts of creatine (0.005 Gm.) daily. M. S. (table 2), P. V. (table 1) and E. L. (table 3) likewise eliminated only small amounts of creatine, although important groups of muscles were affected. The amount of muscular disability in these

TABLE 5.—*Effect of Ingested Creatine and Aminoacetic Acid on Excretion of Urinary Creatine and Creatinine in Patients with Charcot-Marie-Tooth Peroneal Muscular Atrophy*

Patient	Days in Period	Total Urinary Nitrogen Daily, Gm.	Urinary Creatinine Daily, Gm.	Urinary Creatine Daily, Gm.	Aminoacetic Acid per Day, Gm.	Creatine		Creatinine Index, Mg. of Creatinine per Kg. of Body Weight
						Given, Gm.	Retained, %	
Case 4, A. C., male, age 26, 67 Kg.	4	9.43	1.851	0.007				
	2	8.38	1.863	0.108	..	1.32	80	
	4	11.72	1.788	0.105	20	....	..	27.6
	2	11.78	1.913	0.126	20	1.32	96	
Case 5, L. G., male, age 17, 52 Kg.	(1936)							
	4	9.62	1.455	0.035				
	1	9.80	1.500	0.123	..	1.32	91	
	2	9.90	1.403	0.011				
	4	13.00	1.445	0.016	20			
	1	12.55	1.478	0.182	20	1.32	82	28.2
	3	13.55	1.444	0.005	20			
	(1937)							
	1	9.92	1.660	0				
	1	9.36	1.612	0.075	..	1.32	92	
Case 6, G. R., female, 9 yr., 31 Kg.	1	5.88	0.721	0.011				
	1	8.02	0.844	0.384	..	1.32	63	25.2

TABLE 6.—*Effect of Ingested Creatine and Aminoacetic Acid on Excretion of Urinary Creatine and Creatinine in a Patient Immediately Following Acute Anterior Poliomyelitis*

Patient	Days in Period	Total Urinary Nitrogen Daily, Gm.	Urinary Creatinine Daily, Gm.	Urinary Creatine Daily, Gm.	Aminoacetic Acid per Day, Gm.	Creatine		Creatinine Index, Mg. of Creatinine per Kg. of Body Weight
						Given, Gm.	Retained, %	
Case 7, M. W., female, age 8, 23.5 Kg.	4	4.06	0.326	0.048				
	2	4.91	0.316	0.212	..	1.32	67	
	1	3.15	0.347	0.045	..	....	..	13.8
	4	6.92	0.366	0.043	10			
	2	7.47	0.399	0.409	10	1.32	26	
	1	6.97	0.338	0.100	10			

persons was considerable. On the other hand, the wasting was limited to certain groups of muscles which, in spite of their great importance to the patient, represented only a small portion of the total muscle mass of the body. In contrast, H. P. (table 4), who exhibited clinical evidence of extreme wasting of most of the striated muscles, subsequent to acute "neuronitis," excreted an average of 0.244 Gm. of creatine daily. Similarly, E. F. (table 1), whose muscles were extensively involved, had a high spontaneous output of creatine.

E. F., a man aged 52, suffered from weakness and wasting of the muscles subsequent to progressive disease of the anterior horn cells. When he was first seen, in 1935, he had considerable wasting of the muscles of the hands, forearms and lower extremities, but other muscles were not affected. At that time the daily output of creatine was only 0.043 Gm. The course of the disease was one of steady progression. The weakness and wasting of the muscles affected increased, and other voluntary muscles became involved. One year later most of the striated muscles of the body showed extreme weakness and wasting. The creatine output at this time was 0.63 Gm., amounts as large as those eliminated by patients with far advanced and extensive progressive muscular dystrophy.

Creatine Tolerance.—Five of the 12 patients showed some impairment in ability to retain ingested creatine. On the other hand, 7 patients had a creatine tolerance comparable with that seen in most normal subjects. Even when there was appreciable wasting of some important muscle groups the retention of exogenous creatine did not seem to be impaired. Thus, L. G. (table 5) had definite wasting and weakness of the muscles of the feet, calves and hands; yet the creatine tolerance was practically normal—92 per cent. Likewise, A. L. (table 1) and P. V. (table 1) showed extensive involvement of important muscles, but the ability to retain ingested creatine was only moderately impaired. E. F. (table 1), with considerable wasting of the muscles of the hands and legs, had a creatine tolerance of 84 per cent. About one year later, when most of the voluntary muscles of the body were involved, the creatine tolerance was only 15 per cent. An equally serious defect in the creatine tolerance was observed in H. P. (table 4), who excreted all of an ingested dose of creatine (creatine tolerance, 0). The muscular involvement in this patient was severe and extensive; practically every visible muscle was wasted and weak.

The muscular involvement in both patients (E. F. and H. P.) was as extensive and severe as is seen in advanced progressive muscular dystrophy. The creatine tolerance was as seriously affected as in the advanced stages of this disease.

Output of Preformed Creatinine.—Most of the patients in this series had a diminished output of creatinine. In a few instances, e. g., A. B. (table 3) and P. L. and J. B. (table 2), the diminution was slight. However, the "creatinine index" [4] of these patients was somewhat lower than was usually observed in normal persons of the same weight, build and sex (from 19 to 22). The patients showing such minor defects in the excretion of creatinine had muscular wasting restricted to a few groups of muscles. A. C. (table 5) had a creatinine index of 27.6. This high value is explained by the excellent development of the muscles, except those of the peroneal group, which were wasted and weak.

4. The creatinine index is expressed as the number of milligrams of daily preformed urinary creatinine per kilogram of body weight.

Patients who had more extensive muscular wasting also had a lower output of creatinine and a lower creatinine index, e. g., E. L. (table 3), M. S. (table 2) and H. S. (table 1). In instances in which many groups of muscles were seriously involved the excretion of creatinine was reduced considerably. Thus, E. F. (table 1) excreted only 0.72 Gm. of creatinine daily at the time that much of the striated musculature was affected. One year previously, when the wasting was limited to the muscles of the hands and lower extremities, the daily output of creatinine was 1.197 Gm. H. P. (table 4), who had the most extreme and extensive muscular wasting of the patients in this series, excreted only 0.231 Gm. of creatinine daily. The creatinine index for this patient was only 5.8. These values are comparable to those for patients with progressive muscular dystrophy with far advanced and extensive muscular wasting.

In the 17 patients studied, the diminution in the creatinine output appeared to be proportional to the amount of muscular wasting and functional disability.

Neither the site of the muscular wasting nor the type of lesion in the nervous system appeared to modify this relationship.

Effect of Aminoacetic Acid on the Output of Creatine and the Creatine Tolerance.—Eleven of the patients in this series were given aminoacetic acid in amounts of from 10 to 40 Gm. daily. In 7 patients the administration of aminoacetic acid was without effect on the urinary output of creatine. However, in 3 patient there was a moderate increase in the amounts of creatine eliminated when aminoacetic acid was ingested. The effect of aminoacetic acid appeared not to be related to the level of the spontaneous output of creatine, since 2 patients who excreted only about 0.005 Gm. of creatine daily showed an increase of about 0.1 Gm. in the creatine output when aminoacetic acid was given. In several other patients with a spontaneous output of creatine much higher than that of these patients aminoacetic acid was without effect on the creatine output. In 1 patient with extensive muscular involvement the spontaneous output of 0.244 Gm. of creatine daily was increased to 0.713 Gm. when 20 Gm. of aminoacetic acid was ingested daily.

The effect of aminoacetic acid on the creatine tolerance was studied in 10 patients. In 5 instances the simultaneous administration of aminoacetic acid decreased retention of the ingested creatine. This effect of aminoacetic acid on the creatine tolerance was not proportional to the effect on the level of the spontaneous output of creatine. In 2 patients in whom the ingestion of aminoacetic acid did not affect the spontaneous output of creatine the retention of exogenous creatine was reduced. One patient who spontaneously excreted only 0.005 Gm. of creatine daily,

despite considerable muscular disability, had a creatine tolerance of only 56 per cent. This impaired creatine tolerance was reduced further when aminoacetic acid, in amounts of 20 Gm. daily, was given. Under these circumstances, the equivalent of an ingested amount of creatine was excreted in the urine.

When the administration of aminoacetic acid increased the spontaneous output of creatine it decreased the creatine tolerance. With but 1 exception, this relationship existed in all the subjects in this series. However, reduction of the creatine tolerance by aminoacetic acid was frequently observed in patients in whom the spontaneous output of creatine was not influenced by aminoacetic acid. In all cases, if the disturbance in creatine metabolism was serious enough to result in greater output of creatine with administration of aminoacetic acid, it was assumed to be serious enough to cause a decrease in tolerance. On the other hand, the defect in creatine metabolism might be of an order that would show itself in decreased tolerance after administration of aminoacetic acid without being severe enough to result in increased spontaneous output of creatine. These findings are in general agreement with those observed in cases of progressive muscular dystrophy. In the latter condition the ingestion of aminoacetic acid often reveals a magnitude of defects in the metabolism of creatine not shown by the spontaneous output of creatine or the creatine tolerance (Milhorat and Wolff [3]). In patients with muscular wasting subsequent to disease of the spinal cord or peripheral nerves, a gross defect in the metabolism of creatine not otherwise apparent can sometimes be demonstrated by the administration of aminoacetic acid. In the main, in these patients there is involvement of many muscle groups but the muscular defect is not sufficiently generalized to affect seriously the spontaneous creatine output and the creatine tolerance.

COMMENT

Most of the patients excreted amounts of urinary creatinine that were less than those eliminated by normal persons of the same age, sex and apparent muscular development. Patients in whom the wasting of the muscles was slight and confined to a few groups excreted practically normal amounts of creatinine. In contrast, patients who showed extreme wasting of the entire striated musculature excreted amounts of creatinine comparable with those observed in patients suffering from progressive muscular dystrophy with widespread muscular wasting. We [2] have shown that in patients with progressive muscular dystrophy the amounts of creatinine excreted are proportional to the amount and efficiency of the remaining muscles. In normal persons the excretion of creatinine bears a definite relation to the mass and efficiency of the

muscles (Shaffer [5]). In patients with moderate wasting the reduction in the creatinine output was likewise moderate. This interpretation is in agreement with the data obtained in studies previously made on patients with similar conditions (Levene and Kristeller;[1] McCrudden and Sargent;[6] Bürger;[7] Meyer;[8] Gibson, Martin and Buell;[9] Cameron and Gibson;[10] Milhorat;[11] Kostakow;[12] Gros;[13] Harris and Brand;[14] Tripoli and Beard;[15] Cuthbertson and Maclachlan,[16] and Allinson, Henstell and Himwich [17]).

Since in these diseases the loss in functional capacity of the muscle is directly proportional to the amount of wasting, one is justified in stating that there is a definite relation between the loss of muscle mass and the decrease in the output of preformed creatinine. Furthermore, the relation appears to exist regardless of whether the site of the disease process is in the spinal cord or the peripheral nerves.

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5. Schaffer, P. A.: The Excretion of Kreatinin and Kreatin in Health and Disease, Am. J. Physiol. **23**:1, 1908.

6. McCrudden, F. H., and Sargent, C. S.: Chemical Changes in the Blood and Urine in Progressive Muscular Dystrophy, Progressive Muscular Atrophy and Myasthenia Gravis, Arch. Int. Med. **21**:252 (Feb.) 1918.

7. Bürger, M.: Beiträge zum Kreatininstoffwechsel: II. Die Kreatin- und Kreatininausscheidung bei Störungen des Muskelstoffwechsels, Ztschr. f. d. ges. exper. Med. **9**:361, 1919.

8. Meyer, E. C.: Ueber Kreatin- und Kreatininausscheidung bei Krankheiten, Deutsches Arch. f. klin. Med. **134**:219, 1920.

9. Gibson, R. B.; Martin, F. T., and Buell, M. V. R.: A Metabolic Study of Progressive Pseudohypertrophic Muscular Dystrophy and Other Muscular Atrophies, Arch. Int. Med. **29**:82 (Jan.) 1922.

10. Cameron, A. T., and Gibson, A.: Creatinuria in Certain Disease Conditions, Canad. M. A. J. **12**:393, 1922.

11. Milhorat, A. T.: Ueber die Behandlung der progressiven Muskeldystrophie, und ähnlicher Muskelerkrankungen mit Glykokoll, Deutsches Arch. f. klin. Med. **174**:487, 1933.

12. Kostakow, S.: (*a*) Beitrag zur Glykokollbehandlung der neuralen Muskelatrophie und dystrophischen Myotonie, Med. Klin. **30**:1127 (Aug. 24) 1934; (*b*) Ueber Spontankreatinurie bei Nervenerkrankungen, Deutsches Arch. f. klin. Med. **178**:387, 1936.

13. Gros, W.: Der Kreatin-Kreatininstoffwechsel bei spinaler Kinderlähmung und seine Beeinflussung durch Glykokoll, Ztschr. f. klin. Med. **126**:152 1933.

14. Harris, M. M., and Brand, E.: Metabolic and Therapeutic Studies in the Myopathies, with Special Reference to Glycine Administration, J. A. M. A. **101**: 1047 (Sept. 30) 1933.

15. Tripoli, C. J., and Beard, H. H.: Muscular Dystrophy and Atrophy: Clinical and Biochemical Results Following the Oral Administration of Amino-Acids, Arch. Int. Med. **53**:435 (March) 1934.

16. Cuthbertson, D. P., and Maclachlan, T. K.: The Treatment of Muscular Dystrophy with Glycine, Quart. J. Med. **3**:411, 1934.

17. Allinson, M. J. C.; Henstell, H. H., and Himwich, H. H.: The Influence of Glycin on Creatinuria in Peripheral Neuritis, Am. J. M. Sc. **188**:560, 1934.

The output of urinary creatine was moderate or only minimal in most of the patients. Only the patients whose muscles were extensively involved had a high spontaneous output of creatine. Even when the degree of muscular disability in this group approached that observed in some patients with progressive muscular dystrophy the amount of creatine eliminated was small. Thus, H. S. (case 8), with progressive weakness and wasting of the muscles secondary to chronic anterior poliomyelitis, excreted only negligible amounts of creatine (0.005 Gm.) per day. Patients with progressive muscular dystrophy who had similar amounts of disability were shown in the earlier report [2] to have a considerable output of creatine. Observations made by other workers on the elimination of creatine by patients with muscular wasting subsequent to disease of the nervous system have shown that a low output of creatine is usually found even in patients with considerable muscular disability (Levene and Kristeller; [1] McCrudden and Sargent; [6] Bürger; [7] Meyer; [8] Gibson, Martin and Buell; [9] Cameron and Gibson; [10] Milhorat; [11] Kostakow; [12] Harris and Brand; [14] Tripoli and Beard; [15] Cuthbertson and Maclachlan,[16] and Allinson, Henstell and Himwich [17]). The high values for creatine reported by Gros [13] cannot be interpreted, since no clinical data were presented. However, on the basis of the output of creatinine, e. g., 0.39 Gm. for a patient aged 34 with muscular wasting secondary to poliomyelitis, the loss of muscle mass must have been extensive.

In most patients with muscular wasting secondary to disease of the cord or peripheral nerves the muscular involvement is more limited in extent. Even when the process is extensive, fibers in good condition lie side by side with degenerated muscle. Frequently, the ability of these patients to retain exogenous creatine shows no impairment, possibly because the remaining normal muscles are able to fix the ingested creatine. For example, A. L. (table 1), who had considerable wasting of the muscles about the shoulders and whose condition resembled that of many patients with progressive muscular dystrophy, excreted no creatine spontaneously and had a creatine tolerance of 76 per cent. Whether the healthy muscles are likewise able to retain some of the creatine lost by the diseased muscles cannot be demonstrated. Such a postulation may explain the low degree of creatinuria observed in some patients with extensive wasting secondary to disease of the peripheral nerves and anterior horn cells.

On the other hand, when most of the striated muscles are involved the amount of creatine eliminated may equal that of many patients with progressive muscular dystrophy. For example, E. F. (table 1) and H. P. (table 4), in whom the wasting involved the major part of the striated musculature, had creatine excretion of 0.63 and 0.244 Gm. per

day, respectively. Observations on the creatine tolerance and the effect of aminoacetic acid furnish additional evidence of similarity between the extent of the disturbance in the metabolism of creatine in the patients in this series and that in many persons with progressive muscular dystrophy. In patients in whom the wasting was limited to muscle groups representing only a fraction of the entire voluntary musculature of the body the ability to retain ingested creatine was only slightly or moderately impaired. On the other hand, when the disease process had come to involve many of the striated muscles the creatine tolerance was less. In the main, the effect of aminoacetic acid on the creatine output and the creatine tolerance was of the same order; that is, patients with muscular defects involving many groups of muscles showed a greater effect of aminoacetic acid than did those in whom the wasting was limited to a few muscles, although the clinical disability may have been similar in the two groups.

It appears from the data in this report that the creatine tolerance is a better index of the amount of muscular involvement than is the spontaneous output of creatine. Likewise, in progressive muscular dystrophy we [2] found this to be the case. However, neither the creatine output nor the creatine tolerance associated with muscular wasting subsequent to disease of the nervous system appears to be a valuable index of the amount of muscular involvement. The results of this investigation show that considerable wasting and functional impairment of important muscle groups can occur with little effect on the metabolism of creatine. If, however, the creatine tolerance is considered as being dependent on the amount of remaining healthy muscle tissue, the relationship becomes clear. As long as a large portion of the striated musculature remains intact the ability to retain ingested creatine is little affected. The same mechanism probably accounts for the low degree of creatinuria observed in such patients. It is likely that the creatine which would otherwise be eliminated as the result of muscular involvement is retained by the remaining healthy muscles, as is the ingested creatine. When, however, most of the striated muscles of the body are involved, the amounts of creatine eliminated are large and the creatine tolerance is low. Hence, a process seriously involving a limited number of muscle groups but leaving intact other large groups affects the creatine tolerance and the creatine output only slightly, whereas when the muscular wasting involves practically every muscle group the creatine tolerance is much impaired and the output of creatine is considerable. The metabolism of creatine and creatinine in patients with widespread muscular wasting subsequent to disease of the nervous system resembles that observed in patients with advanced progressive muscular dystrophy.

SUMMARY

In patients with muscular wasting associated with disease of the spinal cord or of the peripheral nerves, the diminution in the output of creatinine appears to be directly proportional to the reduction in muscle mass. The amounts of creatine eliminated are smaller than are observed in patients with progressive muscular dystrophy with similar amounts of apparent wasting. Furthermore, the impairment in the creatine tolerance is less than in similarly incapacitated patients with progressive muscular dystrophy. Often, because of the importance of the muscles involved, the degree of disability can be considerable, although these muscles may represent only a small portion of the entire muscle mass of the body. Unless the muscular wasting is extensive, administration of aminoacetic acid is without effect on the output of creatine or the creatine tolerance. However, when the muscular involvement is so extensive as to include most of the skeletal muscles there may occur defects in the metabolism of creatine and creatinine of a magnitude equaling that seen in advanced stages of progressive muscular dystrophy.

REPORT OF CASES

Peripheral Neuritis (table 2).—Case 1.—M. S., a peddler aged 48, entered the New York Hospital on Sept. 10, 1932, complaining of weakness of the hands and feet of four years' duration. In 1913 an operation for correction of hammer toe had been performed. In 1929 gradually increasing weakness of the left hand and foot was first noted. In both feet, pain in the fourth and fifth toes, radiating up to the knee, became increasingly severe. In the little finger of the left hand and the toes of both feet contractures gradually developed. The family and the past personal history were unimportant except that the patient had been addicted to alcohol for several years.

Examination revealed atrophy of the intrinsic muscles of both hands, more evident in the left. There were similar atrophy, as well as gross deformity, of both feet and progressive atrophy of the muscles of the calves and forearms. The proximal portions of the upper and lower extremities on both sides seemed to be well preserved. There was no sensory defect in any part of the body except absence of vibration perception in the toes and legs. The weight was 58 Kg.

Case 2.—J. B., an ice truck driver aged 44, entered the New York Hospital on Nov. 19, 1934, complaining of numbness and tingling of the fingers and toes. In addition, he had a feeling of coldness in the lower portion of the arms and legs and occasionally a "binding" sensation about and above the knees. The legs and feet felt stiff and "wobbly." He had similar numbness and tight feeling in the perineum. In October 1933 the numbness and tingling had started in the right little finger and soon spread to involve the middle fingers of that hand. In May 1934 perineal numbness and loss of sexual sensations were noted. The past personal history was otherwise of no interest. The family history was irrelevant.

Examination revealed no evidence of disturbances in motility, although the ankle jerks were somewhat reduced. The strength of the muscles in the distal portions of the upper and lower extremities on both sides was slightly reduced. The

patient perceived pinprick, cotton wool and vibration less clearly over these areas. In the subsequent six months he gradually improved, but with a slight residue of the tingling sensations in the fingers. The weight was 78.2 Kg.

CASE 3.—P. L., a man aged 24, a student, entered the New York Hospital on April 23, 1934, complaining of weakness of the right hand and arm of six years' duration. In 1927 he had noticed swelling of the right hand, which became worse in cold weather. This was followed by weakness of the hand with atrophy of the intrinsic muscles. In 1930 the right fifth cervical rib was resected. Except for recurrent disturbances in mood in the paternal grandfather, father and two sisters of the father, the family history was not of interest. The past personal history was noncontributory.

Examination on admission showed marked atrophy of the flexor and extensor muscles of the right forearm and the intrinsic muscles of the hand. The right hand was not as warm as the left. No sensory disturbances or other defects in motility were apparent. The weight was 53.2 Kg.

Charcot-Marie-Tooth Peroneal Muscular Atrophy (table 5).—CASE 4.—A. C., a plumber aged 26, a Polish Jew, entered the New York Hospital in August 1934, complaining of a limp and "slapping of the left foot" against the pavement when he walked. He had had these difficulties since 1932. In addition and subsequent to this initial complaint, he suffered from progressive weakness and wasting of the muscles of the lower portions of both legs and of the feet. He tired easily on walking and could not stand without support. It was noted that the eyeballs were becoming prominent. The past personal history was otherwise irrelevant. The history of anterior poliomyelitis was denied, and metal poisoning seemed unlikely. The family history was of no interest except that the paternal grandmother began to suffer from "trouble with her feet" at the age of 65 and remained in bed until her death, at the age of 77.

Examination revealed that the patient when standing erect presented a "stork-like" appearance. The muscles below the knees were atrophied, the muscles of the calves tapering to a minimum just above the ankle. Flexion of the feet was most impaired, but extension was moderately good. The muscles of the thighs were large and strong. The knee jerks were present, but the ankle jerks were not elicited. Perception of a vibrating tuning fork over the distal portions of the lower extremities was reduced. The abdomen and upper extremities were in no way unusual. The weight was 67 Kg.

CASE 5.—L. G., a youth aged 16, of Italian descent presented himself for examination with the following history. Four years previously, at the age of 12, he noted a tendency to invert the left foot while walking, so that he walked on the outside of the sole. This condition progressed, and soon after there developed a shuffling gait and foot drop bilaterally, with wasting of the calf muscles. The feet became weak and deformed, and the muscles of both calves were observed to be smaller. The weakness of the muscles and the difficulty in walking progressed, but for the year prior to his admission the symptoms appeared to be stationary. However, during this period the grip of the hands had become less powerful. The patient's mother, two maternal aunts, two cousins and his maternal grandfather had had difficulty in walking due to weakness of the feet. The past personal history was noncontributory.

Examination revealed the difficulty in walking of which the patient complained. Gait was uncertain. The feet appeared to hang loosely when he walked and were brought to the floor with a slap. The left foot was held inverted, and the

heel did not touch the floor. The muscles of the feet were weak and wasted. All movements of the feet were restricted, and power was much diminished. There was a definite foot drop bilaterally, with some inversion of both feet, more definite on the left side. The peroneal muscles were wasted and weak. The muscles of the thighs showed moderate weakness and wasting. Numerous fibrillations were seen over both thighs and calves and were easily increased by striking the muscles. There were moderate wasting and loss of power of the muscles of both hands. The ulnar eminences were wasted, and the interosseal muscles of both hands were weak and small. In contrast, the muscles elsewhere were exceedingly well developed. The muscles of the shoulder girdle and upper portions of the arms were large and powerful, and the platysma muscles were well developed. The axillas were dripping with perspiration. Over both upper extremities occasional fibrillations were seen. The feet were slightly cyanotic and felt cold to both the patient and the examiner. The biceps and triceps tendon reflexes on both sides were reduced. The knee and ankle jerks were absent, and the plantar reflexes were of flexor type. The abdominal and cremasteric reflexes were normal. No sensory defect could be detected anywhere. No tenderness was elicited when the peripheral nerves were palpated. A roentgenogram of the spine revealed that the fifth dorsal vertebra had a congenital projection and a false articulation with the lower rib. The Kline and Wassermann reactions of the blood were negative. The past personal history was noncontributory. The weight was 52 Kg.

Case 6.—G. R. (a cousin of L. G.), a girl aged 9 years, had complained of progressive weakness of the feet for two years. When she walked the right foot slapped slightly on the floor. The left foot showed a moderately high arch; both feet were held in a moderate "foot drop" position. There were slight wasting of the muscles of both feet and questionable wasting of the peroneal muscles. The muscles of the trunk, upper extremities and thighs were well developed and strong. The muscles of the hands showed no wasting. The deep tendon reflexes of the upper extremities and the abdominal reflexes were normal. The knee jerks were much diminished, and the ankle jerks were absent. The plantar reflexes were flexor in type. No fibrillations were noted, even after repeated mechanical stimulation of the muscles. The perception of light touch, vibration and pain was normal everywhere. The weight was 31 Kg.

Acute Anterior Poliomyelitis (table 6).—Case 7.—M. W., a girl aged 8 years, was admitted to the New York Hospital on Aug. 9, 1935, with complaints of fever, headache, backache and malaise of a few days' duration. She had difficulty in movements of the head and a nasal quality of speech. The family and past personal histories were irrelevant.

Examination at the time of admission revealed absence of the gag reflex, nasal speech and regurgitation of water through the nose. Paresis of the left side of the face was also noted. Muscular weakness elsewhere was not apparent. The weight was 23.5 Kg.

Progressive Anterior Poliomyelitis (table 1).—Case 8.—H. S., a clerk aged 39, was admitted to the Bellevue Hospital [18] on March 8, 1933, complaining of generalized weakness. At the age of 3 years he had had acute anterior poliomyelitis, which affected the left leg. There was moderate residual wasting of the muscles of the leg, which was not, however, sufficient to interfere with his normal activities. Six months before admission he had noticed increasing weakness of the right

18. From the Neurological Service of Dr. Foster Kennedy, who allowed us to publish the notes in this case.

leg. As this progressed, the muscles of the leg became wasted, and the weakness extended to involve the muscles of the back. The patient perspired easily, felt "nervous" and lost from 15 to 20 Kg. At the age of 23 he had "influenza." The family history and the past personal history were otherwise irrelevant.

Examination showed considerable wasting of all the muscles of the lower extremities. The sternocleidomastoid muscles were weak and the masseters wasted. Numerous fibrillations were seen in the muscles of the extremities, trunk and head. Diminution of sensation of the glove and stocking type was present in all four extremities. The right knee jerk was active and the left absent; the ankle jerk was absent on both sides. Because of the excessive perspiration and loss of weight, exophthalmic goiter was also suspected. However, the basal metabolic rate was —13 per cent. Administration of iodine had no effect on the creatine output or creatine tolerance. The weight was 65 Kg.

CASE 9.—P. V., a retired electrical contractor aged 67, was admitted to the New York Hospital on Dec. 4, 1933, complaining of lack of strength in the hands and drooping of the left eyelid. Two years before he had first noted inability to lift the left eyelid. A year later weakness of the left hand developed. He grew rapidly worse in the three weeks preceding admission, and during that time the legs became involved. On admission he was unable to write, button his clothes or put on his coat. The family and past personal history were unimportant.

Examination revealed hyperactive reflexes throughout. The plantar reflexes were flexor in type. There were general muscular wasting and weakness, especially apparent in the extensor muscles of the arms and legs. Sensation was probably not impaired. Early in February 1934 he began to have difficulty in swallowing, and on February 22 he died, presumably of respiratory failure. The weight was 46 Kg.

CASE 10.—K. P., a housewife aged 25, entered the New York Hospital on Sept. 1, 1933, complaining of weakness and twitching of the muscles of the left hand and forearm. Three years before progressive weakness of the left hand and twitching in the muscles of the forearm and fingers had begun. Cramps in the affected arm occurred occasionally. The patient was of the opinion that this had become worse during the last three years. At the age of 6 years she had had "epidemic fever" (poliomyelitis?). The mother had "fits of self destruction," but otherwise the family and the past personal history were irrelevant.

Examination revealed the left arm to be weak, especially in the distal muscles. There was atrophy of the flexor and extensor muscles of the left hand at the wrist, as well as of the intrinsic muscles of the hand. All the tendon reflexes of the left arm were reduced. The right arm may also have been slightly smaller than usual, especially in the distal portion. No other motility or any sensory defect was noted. The weight was 51 Kg.

CASE 11.—E. F., a business man aged 52, was first admitted to the New York Hospital on Jan. 23, 1935, complaining of weakness of the upper and lower extremities. He had first noted weakness of the fingers in December 1933, when attempting to tie a bow. The onset was insidious, and the weakness progressed. In March 1934 he observed wasting of the hands, particularly the right. On Jan. 1, 1935, because of weakness and unsteadiness, he fell down stairs and was unconscious for several minutes. In 1893, at the age of 10 years, he had had diphtheria, which was followed by paralysis of the palate and weakness of the legs, lasting for six months. One year before the onset of the present complaint

he had herpes zoster. There was no history of contact with metals. The family history was noncontributory.

Examination revealed atrophy of both hands and arms, which appeared to be ascending. It was more advanced in the hands, and the fingers were flexed in a clawlike position. The outstretched arms became fatigued easily and showed wrist drop and tremor. The legs also showed some wasting and atrophy, but the patient stated that he always had had small muscles. There were constant fibrillary twitchings throughout the extremities, which were more marked in the upper parts of the legs than in the arms. The knee jerk was slightly diminished on the left. The plantar reflexes were flexor in type. Because of his weakness the patient could not raise himself from a recumbent position without assistance. There was no change in superficial or deep sensation. The weight was 64 Kg.

Subsequent Course: The patient became progressively weaker, with gradual extension of the disease process to other groups of muscles. The muscles affected showed evidence of increasing wasting and weakness, and the patient became confined to bed. About two months prior to his second admission he began to have difficulty in respiration. In April 1936 he was readmitted to the hospital. Examination disclosed advanced wasting of most of the striated muscles of the body. Muscular weakness was extreme, and only a few minor movements could be made. On April 27, 1936, the patient had increased respiratory difficulty and died.

Case 12.—A. L., a quarry worker aged 37, a Spaniard, was admitted on Jan. 30, 1936, complaining of weakness of the shoulders and arms for twelve years. Prior to onset of the presenting symptoms he had been exceptionally strong. Twelve years before his admission he had noted increasing weakness of the upper portions of the arms and the shoulders. One month later he noticed definite wasting of the muscles of the shoulders and the upper parts of the arms and, because of the increased muscular disability, had to discontinue his work. There was no evidence of preceding or accompanying infection. No symptoms were apparent other than those described. Since, the muscular disability seemed not to have increased. The past personal and family histories were noncontributory.

Examination showed advanced wasting of all the muscles of the shoulder region and of the deltoid, biceps and triceps muscles. There was definite winging of the scapulas. The arms could be raised to a level only about midway between the waist and the shoulder. The wasting and disability of these groups of muscles resembled closely those seen in many patients with progressive muscular dystrophy. However, no weakness or wasting of any other muscles could be demonstrated. The forearms were powerful, and the lower extremities were strong and well developed. The biceps tendon reflexes were absent; the triceps tendon reflexes were much diminished. Elsewhere, the reflexes were normal. Occasional fibrillations of the tongue and of the wasted muscles were seen. There was no wasting of the tongue. The weight was 73 Kg.

Case 13.—C. P., a German caretaker aged 61, was admitted to the hospital on May 4, 1936, complaining of weakness of all extremities of one year's duration. He had previously enjoyed good health and had been in the habit of frequently taking long walks. About a year before his admission he noted a sensation of numbness in the right leg. This was accompanied by weakness of the extremity. Both the muscular weakness and the sensation of numbness continued, and a few months later the right arm was similarly affected. Four months before his admission the left leg became weak and numb, and about one month later the left

arm became involved. There were no other abnormal sensations. The sensation of numbness persisted, and the weakness of the extremities progressed steadily, so that he had to discontinue his work and could walk only with the aid of a cane. Activities such as those entailed in dressing himself, shaving and walking became increasingly difficult, and later impossible. Aside from flattening of the thenar eminence of both hands, no muscular wasting was noted. The past personal and family histories were irrelevant.

Examination showed the disability in walking of which the patient complained. There was moderate wasting of the muscles of the upper extremities, which were weak and were fatigued easily. The deltoid, biceps and triceps muscles especially were small and weak. The thenar eminence on both sides was flattened. There were definite wasting, weakness and easy fatigability of the muscles of the thighs and calves. Numerous fibrillary twitchings were seen over all extremities and the front of the thorax. The tendon reflexes were all absent. Over both lower extremities perception of vibration was absent, and over the right hand there was diminished perception of pinprick.

Amyotrophic Lateral Sclerosis (table 3).—Case 14.—A. B., an electrician aged 38, entered the New York Hospital on March 17, 1933, complaining that the left foot hung limp and had not been under good control for nine months (beginning in June 1932). There was no pain. Starting in December 1932, the muscles of both legs, particularly those of the left foot, became tender to the touch. Moreover, the patient had severe muscle cramps in the left leg and foot, which came on particularly at night. There had been gradual progressive weakness and wasting of the left leg, thigh and buttock, and the left leg was usually cold. The family and past histories were irrelevant except that the patient was said to have had a severe fall on his back in 1929.

Examination revealed fibrillation of the muscles of both legs, arms and shoulders and of the back. The tendon reflexes were overactive throughout except for the ankle jerk on the left, which was barely elicited or absent. There was an extensor plantar response on the left; the response on the right was not unusual. No paresthesias or sensory defects were noted. The weight was 84.5 Kg.

Case 15.—E. L., a housewife aged 65, entered the New York Hospital on May 16, 1933, complaining of weakness and wasting of the left arm of two years' duration, which had been especially rapid in its progression during the preceding eleven months. Two years before, after a severe infection of the upper respiratory tract, the patient noted pain in the left heel, accompanied by unsteadiness in walking. Two months later she noted weakness of the arms, particularly the left, which she gradually became unable to raise. One year prior to admission a "heavy feeling" developed in both legs. The family and past personal histories were irrelevant.

Examination revealed that the gait was shuffling. The extensor muscles of the foot were weak. The left arm was wasted and flaccid and weak in all functions, especially on extension. There were atrophy of the left shoulder and the upper and lower portions of the arm and weakness of the extensor muscles of the fingers. The right hand was less affected. The tendon reflexes of the right arm were overactive and those of the left underactive; the right triceps reflex was absent. The tendon reflexes of the right leg were hyperactive and those of the left leg markedly hypoactive. The plantar response of the right great toe was extensor in type. The left thigh measured 46.5 cm. and the right 50.5 cm. There was slurring of speech. No sensory defect could be determined. The weight was 90.2 Kg.

CASE 16.—S. W., an American housewife aged 67, entered the hospital on June 29, 1935, complaining of weakness of the arms and legs. Four years before she had noted increasing weakness of both hands and arms, so that she had difficulty in combing her hair and performing her household duties. About two years later the muscles about the shoulders became involved, and the arms were fatigued rapidly on exertion. One year before her admission she noted that she tripped easily and occasionally fell. The legs soon became weak, and walking became increasingly difficult. For the month or so preceding admission she was barely able to walk at all.

Examination showed considerable weakness and fatigability of the muscles of all the extremities. The patient had difficulty in standing alone, and with support was able to walk only a few short steps. There were moderate wasting and considerable weakness of the muscles of the arms, forearms, thighs and calves. Numerous fibrillary twitches were seen over all four extremities. The biceps and triceps tendon reflexes were absent; the knee and the ankle jerks were hyperactive. The plantar reflex on both sides was flexor in character. The patient was discharged to a convalescent home, where the course was progressively downward and she died on Feb. 18, 1936. The weight was 42 Kg.

So-Called Acute "Neuronitis," of Undetermined Cause (table 4).—CASE 17.—H. P., a housewife aged 28, entered the Bellevue Hospital[18] on July 30, 1933, complaining of complete loss of power in the arms and legs of two weeks' duration. Three weeks before the patient had been ill, with malaise, anorexia and vomiting. These symptoms slowly subsided, so that by the end of the week she felt much improved. Without prodromes she awoke one morning to find the lower parts of the legs and the hands paralyzed. Two days later the upper portions of the arms were involved. Beginning with the onset of the paralysis and lasting for three days, she had severe headache. There were no disturbances in sensation. Except for an attack of cholecystitis in 1931, the past history was noncontributory. The family history was irrelevant.

Examination revealed that the patient was well developed, but poorly nourished. There was bilateral flaccid paralysis of the arms and legs, chiefly in the distal portions. The muscles of the neck were also weak. No abnormalities of sensation could be demonstrated. The anal and vesical sphincters were relaxed, and the patient was incontinent. During the first eight weeks in the hospital she became progressively weaker, and difficulty in swallowing and respiration developed. All the muscles throughout the body were wasted to an extreme degree and were very weak. All the tendon reflexes were absent. The patient was cachectic. After Oct. 15, 1934, she began to improve. The bulbar reflexes returned; motor power was restored in the fingers, and the facial weakness almost disappeared. For the first time sensory changes were noted. There was reduction or loss of all sensation in both legs as far as the middle third of the thighs. Motor function of most of the muscles slowly returned, and the patient regained power to move the arms slightly and to flex the legs. The weight was 40 Kg.

STUDIES IN DISEASES OF MUSCLE

V. METABOLISM OF CREATINE AND CREATININE IN MYOTONIA CONGENITA, MYOTONIA ATROPHICA, AMYOTONIA CONGENITA, DYSTONIA MUSCULORUM DEFORMANS AND PARALYSIS AGITANS

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In the previous reports of this series [1] the metabolism of creatine and creatinine in patients with progressive muscular dystrophy, myasthenia gravis and muscular wasting subsequent to disease of the nervous system was discussed.

In the present study the factors influencing the metabolism of creatine and creatinine in myotonia congenita, myotonia atrophica, amyotonia congenita and dystonia musculorum deformans were investigated. In addition, the effect of muscular activity (tremor) on the output of creatine and creatinine was determined.

MATERIAL AND METHODS

The subjects included 2 patients with myotonia congenita, 4 with myotonia atrophica, 1 with amyotonia congenita, 2 with dystonia musculorum deformans and 1 with paralysis agitans. The methods employed in this investigation were similar to those described in a previous report.[1a] The patients were maintained on a diet free from creatine and creatinine. The urine was collected carefully in twenty-four hour samples, and the urinary creatine and creatinine were determined daily. After a preliminary period as a control, during which the spontaneous excretion of creatine was determined, the patients were given a test dose of 1.32 Gm. of creatine, and the ability to retain the ingested creatine (creatine tolerance) was determined.

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1. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: (*a*) I. Metabolism of Creatine and Creatinine in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **38**:992 (Nov.) 1937; (*b*) II. Effect of Varying Amounts of Ingested Creatine upon the Creatine Tolerance in Progressive Muscular Dystrophy, ibid. **39**:37 (Jan.) 1938; (*c*) III. Metabolism of Creatine and Creatinine in Myasthenia Gravis, Including a Study of the Excretion of Nucleosides and Nucleotides, ibid. **39**:354 (Feb.) 1938; (*d*) IV. Metabolism of Creatine and Creatinine in Muscular Wasting Subsequent to Disease of the Nervous System, ibid., this issue, p. 663.

After a second period of control, the patients usually were given 20 Gm. of aminoacetic acid daily, and the effect of aminoacetic acid on the spontaneous creatinuria and on the creatine tolerance was studied. In most instances the patients were kept in a special metabolism ward, under the supervision of specially trained nurses and dietitians.

OBSERVATIONS

MYOTONIA CONGENITA (THOMSEN'S DISEASE)

The data on the 2 patients with myotonia congenita are presented in table 1. Both patients excreted spontaneously either no urinary creatine or only minimal amounts. On the days when creatine was eliminated, the amounts were no greater than are commonly observed in normal men. When 1.32 Gm. of creatine was given to the patients all the ingested creatine was retained. This finding is similar to that observed in normal men and is in contrast to that seen in patients with pro-

TABLE 1.—*Effect of Ingested Creatine and Aminoacetic Acid on Excretion of Urinary Creatinine and Creatine in Patients with Myotonia Congenita*

Patient	Days in Period	Total Urinary Nitrogen Daily, Gm.	Urinary Creatinine* Daily, Gm.	Urinary Creatine Daily,† Gm.	Amino-acetic Acid per Day, Gm.	Creatine		Creatinine Index‡
						Given, Gm.	Retained, %	
Case 1, R. K., male, age 20, 62 Kg.	4	9.38	1.815	0.050				
	1	9.44	1.800	0	..	1.32	100	
	1	9.42	1.800	0				
	4	12.41	1.886	0.013	20	....	...	28.8
	1	11.48	1.790	0.040	20	1.32	100	
	11	12.41	1.875	0.020	20			
	3	8.54	1.905	0.026				
Case 2, J. D., male, age 30, 72 Kg.	1	10.80	1.620	0.121				
	1	9.43	1.861	0.089	..	1.32	100	
	1	8.90	1.716	0.074				
	5	8.74	1.916	0.051				
	3	12.20	1.728	0.019	20	....	...	25.7
	1	12.20	1.850	0	20	1.32	100	
	1	10.40	1.860	2.050	..	10.00		
	2	9.12	1.875	0.020				

* In this table and in the accompanying tables, daily urinary creatinine is estimated as preformed creatinine.

† In this table and in the accompanying tables, creatine is expressed as creatinine.

‡ In this table and in the accompanying tables, the creatinine index is expressed as the number of milligrams of daily urinary preformed creatinine per kilogram of body weight.

gressive muscular dystrophy, in whom a large percentage of the ingested creatine is excreted in the urine. In neither of the 2 patients with myotonia congenita was the output of creatine or the ability to retain ingested creatine (creatine tolerance [2]) affected by the ingestion of aminoacetic acid. In this respect, also, these patients with myotonia congenita resembled normal men.

Both patients excreted normal amounts of creatinine. The creatinine index [3] was slightly elevated, e. g., 28.8 for R. K. (case 1), whereas the normal subject with muscles of average size has a creatinine index of from 20 to 24. However, both patients had large, well developed muscles. In normal subjects of similar muscular build similar amounts of creatinine are eliminated.

In brief, no abnormality in the metabolism of creatine or creatinine could be demonstrated by the methods employed.

2. The creatine tolerance is the percentage retention of ingested creatine.

3. The creatinine index is the number of milligrams of urinary preformed creatinine per kilogram of body weight excreted daily.

MYOTONIA ATROPHICA (DYSTROPHIA MYOTONICA)

Five of the 6 patients with myotonia atrophica spontaneously excreted slight or only moderate amounts of creatine (table 2). The average daily output of creatine of these 5 patients was about 0.09 Gm. All the 5 patients had definite wasting and weakness of the muscles of the upper and lower extremities, and 1 patient (J. M., case 7) was confined to bed because of muscular disability. Patient H. P. (case 5), fewer of whose muscles were involved, excreted no creatine spontaneously. Two patients had a creatine tolerance of 100 per cent. Three of the 6 patients studied showed only slight impairment in the creatine tolerance (from

TABLE 2.—*Effect of Ingested Creatine and Aminoacetic Acid on Excretion of Urinary Creatinine and Creatine in Patients with Myotonia Atrophica*

Patient	Days in Period	Total Urinary Nitrogen Daily, Gm.	Urinary Creatinine Daily, Gm.	Urinary Creatine Daily, Gm.	Amino-acetic Acid per Day, Gm.	Creatine		Creat-inine Index
						Given, Gm.	Re-tained, %	
Case 3, J. W., male, age 38, 61 Kg.	3	8.77	1.025	0.097				
	2	7.99	0.965	0.247	..	1.32	70	
	5	7.93	0.947	0.087	..	....	..	15.8
	3	11.07	0.881	0.117	20			
	2	11.73	0.894	0.283	20	1.32	67	
Case 4, H. H., male, age 37, 63 Kg.	3	7.66	1.210	0.174				
	2	6.50	1.082	0.162	..	1.32	100	18.0
	2	8.26	1.142	0.082	20			
	2	8.54	1.084	0.075	20	1.32	100	
Case 5, H. P., female, age 18, 56 Kg.	5	7.64	1.092	0				
	5	6.36	1.021	0.173	..	1.5 for 3 days	75	
	2	7.36	1.127	0				
	8	10.62	1.082	0.030	20	....	..	19.3
	4	13.05	1.102	0.088	30			
	5	14.88	1.108	0.706	30	1.5 for 3 days	10	
Case 6, R. A., male, age 48, 53.2 Kg.	2	6.60	0.715	0.062				
	1	8.85	0.691	0.306	..	1.32	76	
	3	6.99	0.683	0.047	..	....	..	13.2
	3	9.82	0.767	0.174	20			
	2	11.66	0.678	0.553	20	1.32	24	
Case 7, J. M., male, age 32, 51 Kg.	2	5.40*	0.800	0.050	..	1.32	36	
	1	4.83*	0.810	0.690				
	4	4.35*	0.765	0.196	..	....	..	15.7
	1	4.87†	0.942	0.152				
	1	7.08†	1.062	0.732	..	1.32	42	
Case 8, A. S., male, age 26, 62 Kg.	1	....	1.965	0.013				
	1	....	1.800	0.190	..	1.32	82	29.8

* The patient had been given 5 grains (0.32 Gm.) of thyroid substance twice a day for six months.

† Two months after last administration of thyroid.

70 to 76 per cent of the creatine was retained). One patient (J. M.) with widespread muscular involvement had a low creatine tolerance (43 per cent). It is of interest that J. M. had been given 10 Gm. of desiccated thyroid gland daily for six months, during his stay at another hospital. The basal metabolic rate was not abnormal. After his transfer to the New York Hospital the thyroid medication was continued until adequate studies could be made to determine the effect of thyroid substance on the metabolism of creatine and creatinine. On discontinuing the administration of thyroid substance no change in the creatine output, the creatine tolerance or the respiratory metabolism was observed.

Four of the 6 patients with myotonia atrophica were given from 20 to 30 Gm. of aminoacetic acid daily. In R. A. (case 6) this increased the spontaneous output of creatine from the control level of about 0.047 Gm. daily to 0.174 Gm. H. P. (case 5), who spontaneously excreted no creatine, eliminated 0.03 Gm. of creatine

daily when 20 Gm. of aminoacetic acid was ingested daily and 0.088 Gm. of creatine when 30 Gm. of aminoacetic acid was taken. During the period when aminoacetic acid was administered the creatine tolerance of both patients was lower than during the periods serving as controls. On the other hand, H. H. (case 4) and J. W. (case 3), who did not excrete larger amounts of creatine when aminoacetic acid was ingested, likewise showed no effect of aminoacetic acid on the creatine tolerance.

All the patients in this series, except A. S., had considerable muscular disability. In each patient important muscle groups were involved, but other groups appeared to be unaffected. In all 6 patients the metabolism of creatine was only slightly or moderately impaired, as evidenced by low spontaneous excretion of creatine and a good creatine tolerance, although 2 patients, J. M. (case 7) and R. A. (case 6), had as much muscular disability as did many patients with progressive muscular dystrophy. In the latter condition, similar degrees of disability commonly are associated with gross defects in the metabolism of creatine.

Four patients (J. W. [case 3], H. H. [case 4], R. A. [case 6] and J. M. [case 7]) excreted less creatinine than usually is eliminated by normal persons of the

TABLE 3.—*Effect of Ingested Creatine and Aminoacetic Acid on Excretion of Urinary Creatinine and Creatine in a Patient with Amyotonia Congenita*

Patient	Days in Period	Total Urinary Nitrogen Daily, Gm.	Urinary Creatinine Daily, Gm.	Urinary Creatine Daily, Gm.	Amino-acetic Acid per Day, Gm.	Creatine		Creatinine Index
						Given, Gm.	Retained, %	
Case 9, A. L., male, age 2½, 11.7 Kg.	5	2.94	0.072	0.149				
	1	2.94	0.073	0.443	..	0.51	23	
	2	2.73	0.069	0.167				
	7	4.17	0.063	0.219	4			
	1	3.53	0.070	0.524	4	0.51*	22	6.15
	2	4.11	0.075	0.232	4			
	2	4.58	0.095	0.303	4			
	1	4.68	0.124	0.648	4	0.51†	7	
	4	3.67	0.075	0.243	4			
	2	3.65	0.115	0.303	4	Regular diet		

* Creatine taken with aminoacetic acid.
† Creatine taken two hours after aminoacetic acid.

same age, weight and sex and had an abnormally low creatinine index. The diminution in the urinary output of creatinine appeared to be of the same order as the diminution in the mass and efficiency of the muscles.

AMYOTONIA CONGENITA (OPPENHEIM'S DISEASE)

The 1 patient in the present investigation with this disease had a daily spontaneous output of 0.149 Gm. of creatine, which was higher than that of the average healthy child of the same age and body weight (table 3). The creatine tolerance, which was 23 per cent, was lower than that of normal children. After the ingestion of 4 Gm. of aminoacetic acid the spontaneous excretion of creatine was increased. In 1 instance in which creatine and aminoacetic acid were taken together, no decrease in the creatine tolerance was observed. However, when the creatine was ingested two hours after the aminoacetic acid the creatine tolerance was decreased from its initial level of 23 per cent to 7 per cent. This phenomenon has been discussed in a previous report.[1a]

The output of creatinine of this patient was definitely diminished. The creatinine coefficient was only 6.15, as compared with a coefficient of from about 14 to 17 for normal children.

DYSTONIA MUSCULORUM DEFORMANS AND PARALYSIS AGITANS

The 2 patients with dystonia musculorum deformans and the 1 patient with paralysis agitans excreted only minimal amounts of creatine (from 0.009 to 0.065 Gm., tables 4 and 5). The amounts of creatine eliminated were no greater than those eliminated by normal subjects or by patients with slight wasting confined to a few groups of muscles.

TABLE 4.—*Effect of Ingested Creatine and Aminoacetic Acid on Excretion of Urinary Creatinine and Creatine in Patients with Dystonia Musculorum Deformans*

Patient	Days in Period	Total Urinary Nitrogen Daily, Gm.	Urinary Creatinine Daily, Gm.	Urinary Creatine Daily, Gm.	Amino-acetic Acid per Day, Gm.	Creatine		Creatinine Index
						Given, Gm.	Retained, %	
Case 10, B. R., female, age 13, 43 Kg.	7	6.24	0.417	0.065				
	4	6.77	0.371	0.242	..	1.5	41	
	10	7.81	0.417	0.053	20			
	4	6.68	0.368	0.324	20	1.5	28	9.4
Case 11, J. W., male, age 17, 40 Kg.	7	....	0.836	0.009				
	3	....	0.765	0.080	15			
	3	....	0.813	0.263	25	...	..	20.0

TABLE 5.—*Effect of Muscular Activity on the Urinary Creatinine and Creatine in a Patient with Paralysis Agitans*

Patient	Days in Period	Total Urinary Nitrogen Daily, Gm.	Urinary Creatinine Daily, Gm.	Urinary Creatine Daily, Gm.	Creatine		Tremor	Total Medication Daily
					Given, Gm.	Retained, %		
Case 12, J. S., male, age 40, 58 Kg.	1	7	1.185	0	....	..	Slight	Scopolamine hydrobromide, 0.018 Gm.; barbital, 0.3 Gm.; phenobarbital 0.06 Gm.
	1	6.73	1.114	0.072	1.32	93	Slight	
	3	7	1.24	0.037	....	..	Slight	
	3	6.9	1.23	0.027	....	..	Considerable	Barbital, 0.3 Gm.
	1	6.87	1.23	0.207	1.32	86	Considerable	
	1	7	1.19	0	....	..	Considerable	

B. R. (case 10), with dystonia musculorum deformans, had a low creatine tolerance. However, much of the reduction in ability to retain ingested creatine was due probably to the age and sex of the patient. Normal girls of the same age (13 years) commonly have a low creatine tolerance. J. W. (case 11), with dystonia musculorum deformans, eliminated increased amounts of creatine when aminoacetic acid was ingested. In the other patient (B. R.) with this condition administration of aminoacetic acid was without effect on the output of creatine. However, ingestion of aminoacetic acid by this patient (B. R.) reduced the creatine tolerance from 41 to 28 per cent. The patient with paralysis agitans had normal creatine tolerance. Both the output of creatine and the creatine tolerance remained unchanged when the adventitious movements were controlled by medication.

The output of creatinine in all these patients was within normal limits.

COMMENT

MYOTONIA CONGENITA, DYSTONIA MUSCULORUM DEFORMANS AND PARALYSIS AGITANS

These syndromes will be considered together, since they represent varieties of pathologically increased muscular contraction.

The conclusion that no abnormal elimination of creatine occurs in myotonia congenita seems to be justified. In 2 cases previously reported by Findlay [4] and Rosenbloom and Cohoe [5] there was likewise no spontaneous output of urinary creatine. Moreover, studies on the effect of ingestion of creatine and aminoacetic acid support the opinion that no demonstrable abnormality in the metabolism of creatine exists.

Poncher and Woodward [6] postulated a relation between the metabolism of creatine and the myotonia in this condition. They observed a decrease in the myotonia when creatinuria was induced by the administration of thyroid and an increase in the myotonia when 1 Gm. of creatine was given by mouth. Under these conditions, diminished elimination of creatine was found invariably to be associated with myotonia. In the studies on J. D. (case 2), which will be published elsewhere, it was found that the administration of 10 and 15 Gm. of creatine was without effect on the patient's symptoms. These results do not seem to confirm those of Poncher and Woodward.

Although the amounts of creatinine eliminated are high, they do not appear to be greater than those excreted by normal persons of the same size, sex and muscular strength (compare the values for the normal subjects M. A. and C. R., used as controls [1a]). The data presented here and those observed in another case by Rosenbloom and Cohoe [5] do not lend support to the conclusion that the creatinine output in myotonia congenita is greater than normal. Patients with myotonia congenita usually have exceptionally well developed muscles, and the high excretion of creatinine is probably dependent more on this factor than on failure of the muscles to relax promptly after contraction. A relation between the excretion of creatinine and "muscle tonus" has been postulated (Pekelharing [7] and Bürger [8]). Aside from the fact that the term

4. Findlay, L.: A Case of Thomsen's Disease, Quart. J. Med. **5**:495, 1912.

5. Rosenbloom, J., and Cohoe, B. A.: Clinical and Metabolism Studies in a Case of Myotonia Congenita: Thomsen's Disease, Arch. Int. Med. **14**:263 (Aug.) 1914.

6. Poncher, H. G., and Woodward, H.: Pathogenesis and Treatment of Myotonia Congenita, Am. J. Dis. Child. **52**:1065 (Nov.) 1936.

7. Pekelharing, C. A.: Die Kreatininausscheidung beim Menschen unter dem Einfluss von Muskeltonus, Ztschr. f. physiol. Chem. **75**:207, 1911.

8. Bürger, M.: Beiträge zum Kreatininstoffwechsel: II. Die Kreatin- und Kreatininausscheidung bei Störungen des Muskelstoffwechsels, Ztschr. f. d. ges. exper. Med. **9**:361, 1919.

"tonus" does not refer to any specific physiologic or clinical entity and hence serves no useful end and may actually confuse the situation (Cobb and Wolff [9]), there are no convincing data that the excretion of creatinine is increased in conditions associated with increased resistance of the muscle to passive stretch or in spastic paralysis. For example, in patients with myotonia congenita or with paralysis agitans (J. S. [case 12]) the amounts of creatinine were not increased. Also, in a case of spastic spinal paralysis associated with muscular wasting reported by one of us (A. T. M.[10]), the output of creatinine was found to be related to the amount of efficiently functioning muscle. No correlation between the elimination of creatinine and the spasticity could be established.

Similarly, in patients with other forms of pathologically increased muscular contraction there is no evident disturbance in the metabolism of creatine and creatinine. Thus, the 2 patients with dystonia musculorum deformans and the 1 patient with paralysis agitans excreted only minimal amounts of creatine, which were comparable with those observed in persons with slight wasting confined to a few groups of muscles.

The lack of influence of muscular activity on the output of creatine in these conditions is further indicated by the studies on the patient with paralysis agitans. No difference in the metabolism of creatine could be demonstrated during two periods of observation, one in which the tremor was practically abolished by medication and the other in which the tremor was uncontrolled. Light and Warren [11] observed that in adolescence the urinary output of creatine is lower during periods of complete rest than during exercise. However, Denis and Kramer [12] found these periodic variations in the elimination of creatine to be related to the hours of feeding, and Rougichitch [13] expressed the belief that the differences in the level of creatine in the urine could be accounted for by fluctuations in the volume of the urine. In the present studies, the diet and the urinary volume were kept constant. Furthermore, the determinations of creatine were made on twenty-four hour specimens

9. Cobb, S., and Wolff, H. G.: Muscle Tonus, Arch. Neurol. & Psychiat. **28**:661 (Sept.) 1932.

10. Milhorat, A. T.: Ueber die Behandlung der progressiven Muskeldystrophie, und ähnlicher Muskelerkrankungen mit Glykokoll, Deutsches Arch. f. klin. Med. **174**:487, 1933.

11. Light, A. B., and Warren, C. R.: Creatinuria Among Adolescent Males, J. Biol. Chem. **104**:121, 1934.

12. Denis, W., and Kramer, J. G.: The Influence of Protein Intake on Creatine Excretion in Children, J. Biol. Chem. **30**:189, 1917.

13. Rougichitch, O. S.: The Day-and-Night Creatinine and Creatine in the Urine of Infants, Arch. Dis. Childhood **1**:289, 1926.

of urine; therefore, the time of feeding was without effect on the determinations. The data on the subjects in this series indicate, moreover, that muscular work is without effect on the daily excretion of creatine. A patient (C. M.) with progressive muscular dystrophy who excreted large amounts of creatine showed no decrease in the spontaneous output of creatine during ten days of complete rest in bed.[1a] The excretion of creatine was the same as that during several weeks of moderate activity and physical therapy.

That muscular activity has no effect on creatine tolerance is suggested by the observations on the patient with paralysis agitans. In this case the ability to retain ingested creatine was the same when the tremor was present as when it was abolished by medication. One patient with dystonia musculorum deformans and vigorous adventitious movements had reduced creatine tolerance. On the other hand, a patient with paralysis agitans had normal creatine tolerance, as well as violent adventitious movements. The diminished creatine tolerance in the patient with dystonia musculorum deformans appeared to be related to the amount and extent of the muscular wasting.

A different attitude was expressed by Levene and Kristeller,[14] who found a lowered creatine tolerance in a patient with continuous tremor. Since the ability to retain creatine was better in this patient than in another with progressive muscular dystrophy, they postulated that in conditions of great muscular activity both the production and the oxidation of creatine exceed the normal limits. On the other hand, they reasoned that the production and oxidation of creatine in progressive muscular dystrophy proceed at a low rate. The data of this study do not support this view. In fact, so far as could be observed, differences in creatine tolerance are not directly related to the amount of muscular activity.

In the 2 patients with dystonia musculorum deformans studied, ingestion of aminoacetic acid was followed by an increase in the elimination of creatine. In the 1 patient in whom the creatine tolerance was determined, ingestion of aminoacetic acid decreased the percentage retention of the ingested creatine. The magnitude of the effects of aminoacetic acid seemed to be dependent on the degree of impairment in the creatine tolerance rather than on the level of the spontaneous output of creatine. It appeared, further, to be of the same order as is commonly observed in patients with slight muscular wasting.

The output of creatinine in the 2 patients with dystonia musculorum deformans was slightly reduced. The patient with paralysis agitans

14. Levene, P. A., and Kristeller, L.: Factors Regulating the Creatin Output in Man, Am. J. Physiol. **24**:45, 1909.

eliminated normal amounts. Both the patients with dystonia musculorum deformans were thin and poorly developed, with small muscles of the lower extremities. Although wasting of the muscles is an unusual feature in dystonia musculorum deformans, its occurrence has been described (Keschner [15]). Histopathologic studies in a case reported by Davison and Goodhart [16] showed definite wasting of certain groups of muscles. The decrease in the output of creatinine in dystonia musculorum deformans, therefore, is probably related to diminution in the mass and functional efficiency of the muscles, and not to the adventitious movements.

Unusual and excessive movement of the muscles does not increase the daily output of creatinine. For example, J. S. (case 12), with violent, coarse tremor of the arms and legs, had a similar output of creatinine before and after the tremor had been greatly reduced by means of scopolamine. These findings are in agreement with previous work which showed that even severe muscular work has no influence on the daily output of creatinine (van Hoogenhuyze and Verploegh,[17] Shaffer [18] and Schulz [19]). Patients with continuous tremor in whom wasting of the muscles develops show no more diminution in the elimination of creatinine than do other patients without adventitious movements and with similar amounts of wasting.

In brief, these findings support the view that delayed muscular relaxation, increased resistance to passive stretch and pathologically increased muscular activity are without effect on the metabolism of creatine or creatinine.

MYOTONIA ATROPHICA

The 6 patients studied in this series excreted slight or moderate amounts of creatine. The amounts of creatine eliminated were comparatively small, even for patients who exhibited considerable weakness of important groups of muscles. A similar moderate output of creatine was observed for patients previously studied by Bürger,[8] Meyer [20] and

15. Keschner, M.: Dystonia Musculorum Deformans, J. Nerv. & Ment. Dis. **47**:103, 1918.

16. Davison, C., and Goodhart, S. P.: Dystonia Musculorum Deformans: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **29**:1108 (May) 1933.

17. van Hoogenhuyze, C. J. C., and Verploegh, H.: Beobachtungen über die Kreatininausscheidung beim Menschen, Ztschr. f. physiol. Chem. **46**:415, 1905.

18. Shaffer, P. A.: Diminished Muscular Activity and Protein Metabolism, Am. J. Physiol. **22**:445, 1908.

19. Schulz, W.: Der Verlauf der Kreatininausscheidung im Harn des Menschen mit besonderer Berücksichtigung des Einflusses der Muskelarbeit, Arch. f. d. ges. Physiol. **186**:126, 1921.

20. Meyer, E. C.: Ueber Kreatin-und Kreatininausscheidung bei Krankheiten, Deutsches Arch. f. klin. Med. **134**:219, 1920.

Kostakow.[21] However, in 1 patient as much as 0.353 gm. of creatine was eliminated daily while the patient was maintained on a diet "practically" free from creatine (Morgulis and Young [22]).

Some observers (Adie and Greenfield,[23] Keschner and Davison [24] and Morgulis and Young [22]) have suggested that the condition may be muscular dystrophy associated with "myotonic" phenomena. This seems unlikely, if one may draw inferences from defects in the metabolism of creatine. In contrast to the findings in progressive muscular dystrophy, the spontaneous output of creatine in this condition is usually small; the creatine tolerance is higher, and the effect of aminoacetic acid on the output of creatine is less. In fact, judged by these three criteria, patients with myotonia atrophica resemble more closely patients with muscular defects secondary to disease of the anterior horn cells and peripheral nerves, with the wasting confined to a few groups of muscle, than persons with more widespread disease of the muscles, such as progressive muscular dystrophy (Milhorat and Wolf).[1a,d]

Four of the 6 patients studied had slight impairment in the creatine tolerance, but 1 patient with extensive involvement of the muscles retained only 42 per cent of the creatine ingested. These values are comparable with those observed in patients with muscular wasting confined to a few muscle groups but with other muscles free from disease (Milhorat and Wolff [1d]). Observations reported on 2 patients with myotonia atrophica showed a creatine tolerance of 20 per cent in 1 (Morgulis and Young [22]) and a more severely impaired tolerance—less than 5 per cent—in the other (Kostakow [21]). The clinical data and the creatinine output indicate that the patients had extensive wasting of most of the striated muscles.

Likewise, the effect of aminoacetic acid on the metabolism of creatine is much less in myotonia atrophica than in progressive muscular dystrophy. It is of the same order as that in patients with muscular wasting confined to a limited number of muscle groups, many of whose muscles are free from disease (as in disease of the anterior horn cells or the peripheral nerves).

In 2 of the 4 patients studied, administration of aminoacetic acid was without effect on the output of creatine. In 1 patient without

21. Kostakow, S.: Beitrag zur Glykokollbehandlung der neuralen Muskelatrophie und dystrophischen Myotonie, Med. Klin. **30**:1127, 1934.

22. Morgulis, S., and Young, A.: Metabolism in Myotonia Atrophica: Report of a Case, Arch. Int. Med. **48**:569 (Oct.) 1931.

23. Adie, W. J., and Greenfield, J. G.: Dystrophica Myotonia (Myotonia Atrophica), Brain **46**:73, 1923.

24. Keschner, M., and Davison, C.: Dystrophica Myotonia: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **30**:1259 (Dec.) 1933.

spontaneous output of creatine, 20 Gm. of aminoacetic acid was without effect, but administration of 30 Gm. daily induced slight elimination of creatine. However, in the fourth patient, with more extensive muscular wasting and slight creatinuria, aminoacetic acid had an appreciable effect on the output of creatine.

Though aminoacetic acid was without effect on the creatine tolerance in some patients, in others the tolerance was lower after the administration of aminoacetic acid than before. In 1 case reported ingestion of 35 Gm. of gelatin (the equivalent of about 7 Gm. of aminoacetic acid) did not affect the output of creatine (Morgulis and Young [22]).

The creatine tolerance, the creatine output and the effect of aminoacetic acid in patients with myotonia atrophica resembled more closely those of patients with muscular wasting subsequent to a lesion of the anterior horn cells or of the peripheral nerves than of patients with progressive muscular dystrophy, myasthenia gravis, or amyotonia congenita. However, this is not justification for inferring that the primary site of the disease is in the spinal cord or the nerves.

The output of creatinine in the 4 patients in this series was slightly reduced. This decrease was greatest in the patients with most marked wasting and disability of the muscles. It was of the same order as that observed in cases already reported (Pemberton,[25] Bürger,[8] Meyer,[20] Kostakow [21] and Morgulis and Young [22]). Furthermore, the decrease in the output of creatinine appeared to be more closely related to the reduction in muscle mass and to weakness than to failure of the muscles to relax promptly after contraction. As already mentioned, Poncher and Woodward [6] observed the induction of creatinuria in a child with myotonia congenita when thyroid was administered. On the other hand, an adult patient with myotonia congenita who was given thyroid substance excreted no creatine. J. M. (case 7), with myotonia atrophica, had been given 10 grains (0.65 Gm.) of thyroid substance daily for six months, up to the time he was admitted to the New York Hospital. No effect of this administration on the creatine output or the creatine tolerance could be demonstrated. After the thyroid had been discontinued for two months, the creatinuria and creatine tolerance were the same as during the period of thyroid administration. These findings in a patient with myotonia atrophica are similar to those observed in normal subjects by Shorr and Richardson,[26] who found that thyroid in amounts up to 2 grains daily (0.13 Gm.) did not induce creatinuria.

In the comment on myotonia congenita, it was demonstrated that the "myotonia" is without effect on the metabolism of creatine and

25. Pemberton, R.: A Metabolic Study of Myotonia Atrophica, Am. J. M. Sc. **141**:253, 1911.

26. Shorr, E., and Richardson, H. B.: Unpublished data.

creatinine. Similarly, in myotonia atrophica the changes that occur in the metabolism of creatine and creatinine appear to be related not to the myotonia but to the associated muscular wasting.

AMYOTONIA CONGENITA

The elimination of creatine in children with amyotonia congenita is considerably in excess of that commonly observed in normal children of about the same age and body weight (from 0.035 to 0.081 Gm.) (Krause,[27] Powis and Raper,[28] Gamble and Goldschmidt [29] and Harding and Gaebler [30]). Creatinuria of a magnitude similar to that in the patient in this series was observed in the 3 patients previously studied by Powis and Raper,[31] Ziegler and Pearce [32] and one of us (A. T. M.).[10]

The output of creatinine in the 1 patient studied was diminished. The creatinine coefficient was only 6.15, as compared with a coefficient of from about 14 to 17 for normal children (Powis and Raper [28]). In the few patients previously studied, similar values were obtained (Spriggs,[33] Gittings and Pemberton,[34] Powis and Raper,[31] Ziegler and Pearce [32] and one of us [A. T. M.][10]). Although in amyotonia congenita the muscles show no obvious wasting but are flaccid and incapable of forceful contractions, the reduction in the output of creatinine is as marked as that for some patients with progressive muscular dystrophy with extensive wasting of the muscles.

While the creatine excreted formed a high percentage of the total output of creatinine and creatine, this percentage was lower than that observed for some patients with progressive muscular dystrophy. Thus, the ratio of creatinine and creatine for the patient with amyotonia congenita was 2.07; for normal children the ratio is from about 0.42 to 0.84 (estimated on the basis of values given by Krause,[27] Powis and Raper [28] and Harding and Gaebler [30]), and for patients with

27. Krause, R. A.: On Age and Metabolism and on the Significance of the Excretion of Creatine, Quart. J. Exper. Physiol. **7**:87, 1914.

28. Powis, F., and Raper, H. S.: Creatinuria in Children, Biochem. J. **10**:363, 1916.

29. Gamble, J. L., and Goldschmidt, S.: A Study of the Creatinuria in Infants: II. Relation of Protein Intake to Urinary Creatine, J. Biol. Chem. **40**:215, 1919.

30. Harding, V. J., and Gaebler, O. H.: The Constancy of the Creatin-Creatinin Excretion in Children on a High Protein Diet, J. Biol. Chem. **57**:25, 1923.

31. Powis, F., and Raper, H. S.: A Study of the Metabolism in a Case of Amyotonia Congenita, Quart. J. Med. **10**:7, 1916-1917.

32. Ziegler, M. R., and Pearce, N. O.: A Metabolic Study of Amyotonia Congenita, J. Biol. Chem. **42**:581, 1920.

33. Spriggs, E. I.: On the Excretion of Creatinin and Uric Acid in Some Diseases Involving the Muscles, Quart. J. Med. **1**:63, 1907-1908.

34. Gittings, J. C., and Pemberton, R.: Metabolic Observations on Amyotonia Congenita, Am. J. M. Sc. **144**:732, 1912.

advanced progressive muscular dystrophy we observed ratios of 3.28 and 5.17.[1a]

The "total creatine coefficient"[35] in this case was 21.87; in the case reported by one of us (A. T. M.[10]) it was 19.32. For the normal children studied by Powis and Raper the total creatine coefficient was 23.72 and 24.7. Cameron and Gibson[36] and Gibson,[37] on the basis of their findings in a case of "muscular infantilism," postulated that the lowered elimination of creatinine results from an increase in the creatine output and that this is due to inability of the muscles to utilize the creatine. They assumed further that the creatine presented to the muscle is formed in some site other than the muscle. Harding and Gaebler[30] presented similar concepts concerning the creatinuria of normal children. On the basis of the data obtained on these patients, the formulation of Cameron and Gibson[36] and Harding and Gaebler[30] appears to be justified. However, as we[1a] have pointed out for patients with progressive muscular dystrophy, the constancy of the total creatine coefficient is more apparent than real.

The daily ingestion of aminoacetic acid increased the spontaneous output of creatine and decreased the creatine tolerance. A similar increase in the excretion of creatine following ingestion of aminoacetic acid by a patient with amyotonia congenita was observed by one of us (A. T. M.).[10]

The 1 patient with amyotonia congenita studied in the present investigation showed a creatine tolerance of only 23 per cent, a value comparable with that observed by one of us (A. T. M.)[10] in another patient with this condition. As compared with the findings in normal children, the reduction in the creatine tolerance is of the same order as the increase in the spontaneous output of creatine. As in other myopathies, both primary and secondary, the lowest tolerance and the greatest output of creatine occur together. In fact, there appears to be an inverse ratio between the creatine tolerance and the spontaneous output of creatine.

SUMMARY

1. In patients with myotonia congenita no abnormality in the metabolism of creatine or creatinine can be demonstrated by the methods employed. Like normal subjects, patients with this condition eliminate no creatine spontaneously, or only minimal amounts. They are able to retain fairly large amounts of ingested creatine. Aminoacetic

35. The "total creatine coefficient" is the sum of the amounts of creatine and creatinine in the urine expressed as the number of milligrams of creatine per kilogram of body weight.

36. Cameron, A. T., and Gibson, A.: Creatinuria in Certain Disease Conditions, Canad. M. A. J. **12**:393, 1922.

37. Gibson, A.: Muscular Infantilism, Arch. Int. Med. **27**:338 (March) 1921.

acid in the amounts used is without effect on the excretion of creatine or the creatine tolerance. The excretion of creatinine is similar to that of normal persons of the same weight, sex and muscular development.

In patients with dystonia musculorum deformans and paralysis agitans there is no obvious impairment in the metabolism of creatine and creatinine. Continuous and vigorous adventitious movements of the muscles are without effect on the elimination of creatinine and creatine and on the creatine tolerance.

Thus, in syndromes representing a variety of pathologically increased muscular contractions, i. e., "myotonia," increased resistance to passive stretch (spasticity) and adventitious movements, there is no effect on the metabolism of creatine and creatinine.

2. In patients with myotonia atrophica the metabolism of creatine and creatinine usually is abnormal. There is diminution in the excretion of creatinine, which appears to be directly proportional to the reduction in muscle mass. Patients with slight or moderate muscular disability have spontaneous creatinuria, although the amounts of creatine excreted are much lower than those for patients with progressive muscular dystrophy showing similar amounts of muscular disability. In fact, in myotonia atrophica moderately severe wasting and disability of important muscle groups can occur with only slight or moderate output of creatine. The creatine tolerance is only moderately impaired and is unaffected by the ingestion of aminoacetic acid. However, by patients showing extreme and extensive involvement of the muscles large amounts of creatine are excreted. The creatine tolerance is then seriously impaired, and the ingestion of aminoacetic acid is followed by an increase in the output of creatine and a further decrease in the ability to retain ingested creatine. In short, in their metabolism of creatine and creatinine patients with myotonia atrophica resemble more closely patients with muscular wasting subsequent to disease of the nervous system than those with progressive muscular dystrophy. These findings, however, do not justify any inference regarding the primary site of the disease in myotonia atrophica.

3. Patients with amyotonia congenita usually excrete considerable amounts of creatine. Moreover, their creatine tolerance is low, and aminoacetic acid increases the amount of creatine excreted and further decreases the creatine tolerance. The output of creatinine is much diminished.

REPORT OF CASES

MYOTONIA CONGENITA (TABLE 1)

CASE 1.—R. K., a man aged 20, a student, entered the New York Hospital on Aug. 21, 1933, complaining of "stiffness of the muscles." He expressed the belief that he had had this disability since infancy. The past personal history was irrele-

vant. As a boy, he had always been exceptionally "muscular." Two members of the family—a sister aged 9 and the father's mother's brother (the patient's paternal granduncle)—had similar disabilities.

Examination revealed that initial movements of the muscles were especially difficult. Contraction was of approximately normal speed, but relaxation was slow. Thus, grasped objects were not readily released. Skilled finer movements were at first impossible, but subsequent movements were more facile. The sternocleidomastoid muscle remained contracted after rotation of the head from side to side. When the patient sneezed, the abdominal muscles remained contracted for a short period after the paroxysm. The tendon reflexes were active. When the belly of the muscle was struck a slow wave of contraction appeared, which began at the site of the blow. Such a reaction was also observed when the tongue was struck. The muscles were well developed, prominent, firm and apparently in a state of sustained, though partial contraction. The patient sweated profusely. The weight was 63 Kg.

Case 2.—J. D., a bus driver aged 30, was admitted to the New York Hospital on March 6, 1934, complaining of muscular rigidity of lifelong duration. Since early childhood the patient had been unable to relax his grasp quickly after initially taking hold of an object. After a few contractions this defect disappeared, only to reappear after a period of rest. He stated that after taking moderate amounts of alcoholic beverages the defect was less evident. A brother, a sister and 2 of his 3 children had a similar disability. The past personal history was not important.

Examination revealed the defect already described. The muscles were well developed and prominent. The patient sweated excessively. The weight was 72 Kg.

MYOTONIA ATROPHICA (TABLE 2)

Case 3.—J. W., dock messenger aged 38, of Irish-American stock, was admitted to the New York Hospital in February 1934. In 1927, at the age of 31, he became aware that his grip was weak and that he could not carry luggage with ordinary ease or sacks of mail except by throwing them over his shoulder. During 1928 and 1929 there developed a shuffling gait, and he became unable to dorsiflex the feet. During the next two or three years he frequently stumbled and fell, until he acquired the habit of raising the feet to an unusual height when walking. If he was cautious and raised the knees he could run. In 1930 the muscles of the neck became weak. From 1931 to 1934 there was progressive weakness of the hands and arms, and at the time of admission the arms hung limply at the side. In 1934 he was unable to flex the left elbow, except by elevating the arm and throwing the hand toward the shoulder. For two years he had been unable to clench the fist of either hand and had had great difficulty in buttoning his collar. It was impossible for him to lift a glass of water to his mouth without unusual pronation and flexion of the wrist. During the two years before his admission to the hospital (from 1932 to 1934) his facial expression had gradually become fixed. His voice had been growing weak for one year. He complained of black spots appearing near the center of the visual field of the right eye. During the preceding year he had noticed occasional difficulty in releasing his knife and fork when using them at meals. The crown and frontoparietal regions of the head had been bald for several years. There had been no change in sexual activity, which had never been great; the power of erection was not lost. There was no family history of muscular disease, paralysis or cataract, and the past history was unimportant.

Examination revealed weakness of the orbicular muscles of the eyes and mouth. The sternocleidomastoid muscles were weak, and there were weakness and atrophy

of the biceps and triceps muscles and the muscles of the forearm. When the patient first attempted a sustained or forceful contraction, as in gripping, prompt relaxation of the muscles was difficult. The hands relaxed slowly. The thighs were apparently normal in appearance and function. There was, however, symmetric atrophy of the muscles of the legs below the knees. There were a large pad of fat over the lower cervical region and a heavy growth of hair over the chest and abdomen. The left testis was smaller than the right; both were perhaps smaller than average, but they were not definitely atrophic. Ophthalmologic examination revealed cataract bilaterally. The patient weighed 61 Kg.

CASE 4.—H. H., a physician aged 37, came under observation on Oct. 12, 1933. At the age of 32 he had noticed that when he walked the left foot made a slapping noise on the ground. Shortly after he experienced progressive weakness and tired easily. About two years after the onset of the symptoms (1930) he noticed that the muscles of the hands after forced contraction relaxed more slowly than formerly and that he had difficulty in releasing grasped objects. The hands became progressively weaker, and after a few months the difficulty in extending the fingers after forceful flexion had almost disappeared. One year before his admission to the hospital he experienced pain in the left leg and more rapid increase in the general muscular weakness, which had been steadily progressing. The extremities had always been thin, and the patient was unaware of any muscular wasting. Friends who had not seen him for several years remarked on the appearance of his face, which had become wasted and expressionless. The hair line on the forehead gradually receded. Eight months before his admission sexual drive began to diminish. There was practically no loss of weight. The past personal and family histories were noncontributory.

Examination on October 12 showed that the patient was well developed, but undernourished. When he walked, the left foot made a slapping sound as it struck the floor. The face was of the "hatchet" type, and there was moderate frontal baldness. The muscles of the face were wasted and the movements feeble. Numerous subcapsular opacities were seen in both lenses on slit lamp examination. The voice had a nasal character. The muscles of all four extremities were weak and slightly wasted. The hand clasp was weak; after forced contraction the muscles of the hand relaxed more slowly than normally. This defect in the relaxation of the muscles disappeared after a few contractions, but reappeared after a period of rest. The patient weighed 63 Kg.

CASE 5.—H. P., a girl aged 16, entered the Cornell clinic on Dec. 23, 1930, complaining of weakness of the lower extremities. Even as a child she was not active on her feet, although she walked, cut teeth and talked at the usual ages. For the two years preceding her admission to the clinic the legs and ankles were definitely weak. She had cramps in the calves and sensations of "pins and needles" in the lower extremities, which were more troublesome in the left leg than in the right. She complained of pain in the hands. The past personal history was otherwise noncontributory. The family history was irrelevant.

Examination revealed steppage gait and weakness and uncertainty in walking. The tendon reflexes were present and active in the upper extremities, but absent in the lower. There were weakness and wasting of the muscles of the feet and of the peroneal groups. Contraction of the muscles of the hands was approximately of normal speed, but relaxation was slow. Grasped objects were not readily released. This delay in relaxation disappeared after a few contractions had been made, but soon reappeared after a period of rest. No change in sensory perception was noted. The patient weighed 56 Kg.

Case 6.—R. A., an Australian elevator operator aged 48, entered the Bellevue Hospital [38] on Nov. 9, 1933, complaining of weakness and difficulty in walking for three years. Since the onset of the symptoms there had been progressive muscular weakness and wasting, with increasing difficulty in walking. For the year preceding his admission to the hospital sexual activity had steadily decreased. The patient walked with a cane. The past history was noncontributory except that up to two years before admission he drank alcoholic beverages in excess. The family history was irrelevant.

Examination revealed bilateral wasting and weakness of the sternocleidomastoid, pectoral and deltoid muscles and weakness of the tibialis muscles. The profile was of the "hatchet" type, and there was weakness of the orbicular muscles of the eyes and mouth and of the masseter and temporal muscles. When the tongue and the muscles of the forearm were struck a slow wave of contraction appeared at the site of the blow. The knee jerks were weak, and the ankle jerks were absent. The Wassermann reactions of the blood and the spinal fluid were negative, but the Kahn reaction of the blood was 4+ and that of the spinal fluid +. The basal metabolic rate was —17 per cent. The patient weighed 53 Kg.; the greatest weight had been 71 Kg., at the age of 36.

Case 7.—J. M., an electrician aged 32, entered the New York Hospital on April 4, 1935, complaining of muscular weakness and reduction in perception of sensation over the arms and legs for a year and a half. Eighteen months before his admission to the hospital there developed weakness of the muscles of the legs. The weakness gradually progressed, and four months later the muscles of the arms became involved. At about the same time (fourteen months before admission) the hands became weak, and the patient noted increasing difficulty in releasing grasped objects. After a forceful initial contraction the muscles of the hands relaxed with difficulty, after a delay of several seconds. Shortly after, similar disability developed in the muscles of the legs and face. At that time the patient complained of a sensation of "pins and needles" in the fingers and toes and of weakness of the muscles of the feet, which made a slapping noise in walking. About thirteen months before his admission to the hospital the patient noted anesthesia below the knees and below the elbows on both sides. He began to lose hair, and frontal baldness developed rapidly. Muscular weakness progressed so that even slight exertion exhausted him. Appetite became poor, and he lost weight. There was difficulty in swallowing food, and often fluids were regurgitated through the nose. The face became "hatchet like" in appearance, and the patient was unable to smile or whistle. He was admitted to the Bellevue Hospital, where he was fed by nasal catheter because of the stiffness of the muscles of the jaw, which could be relaxed only with difficulty, and because of the weakness of the muscles of deglutition. During his stay at the Bellevue Hospital the patient was unable to walk or stand. The muscular weakness persisted and appeared to progress slowly. There was considerable difficulty in relaxing the muscles of the jaws and hands after initial contraction, and the disturbance in sense perception of the extremities remained unchanged.

On April 4 the patient was transferred to the New York Hospital. The family history was noncontributory. At the age of 4 years the patient had had measles and whooping cough; at 9, scarlet fever; at 10, diphtheria, and at 12, typhoid. He had pneumonia at the ages of 14, 15 and 30 years. In 1918, at the age of 16, he had influenza and pneumonia. In 1918, while serving with the American

38. From the neurologic service of Dr. Foster Kennedy, who allowed us to publish the notes in this case.

Army in France, he sustained a gunshot wound in the right ankle. Appendectomy was performed in 1921 (at the age of 19), and tonsillectomy, in 1922 (at the age of 20).

Examination disclosed the disability of which the patient complained. He was thin and poorly nourished and was unable to lift himself into a sitting position in bed. The face was of the "hatchet type," with poor movements. The muscles of the face and extremities were wasted and weak. After an initial contraction the muscles of the jaw and hands could be relaxed only with difficulty. When the hands were clenched the patient was unable to open them for about two minutes. The biceps, triceps, knee and ankle jerks were absent. Below the knees and below the elbows on both sides perception of light touch, pain, temperature, vibration and position and two point discrimination were absent. The patient weighed 51 Kg.

CASE 8.—A. S., a tinsmith's helper aged 24, entered the New York Hospital on Dec. 31, 1936, complaining of stiffness of the muscles and general weakness. The date of onset of the disability was uncertain. He had complained of weakness for many years and had had numerous vague complaints referable to various organs. The muscular stiffness had been moderate and had bothered him only when he had been excited or exposed to cold. The past personal history was irrelevant except for excessive preoccupation with his bodily and spiritual difficulties. A brother aged 22 complained of similar muscular stiffness. Slit lamp examination showed that the brother had subcapsular opacities of the lenses characteristic of myotonia atrophica.

On examination, the face suggested the "hatchet" type. There was moderate frontal baldness. The muscles of the jaw relaxed slowly after forceful closure of the mouth. The hands were thin and of feminine appearance and could be opened only slowly after initial contraction of the muscles. The testes were small. The right foot made a slapping sound when it was brought to the floor in walking. Slit lamp examination of the lenses showed no opacities. Examination of the semen showed no motile or nonmotile spermatozoa.

AMYOTONIA CONGENITA (TABLE 3)

CASE 9.—A. L., a boy aged 2½ years, entered the New York Hospital on July 24, 1933, with a history of flaccidity of the muscles since birth. Although the teeth appeared at the usual time and he began to talk at an early age, the patient had never walked, lifted his head or stood erect. The condition was slowly, but steadily, improving. The family and past personal histories were not important except that the proper nutrition of the patient had been a problem during infancy.

Examination revealed that the child, who was lying in bed, moved the arms and legs freely but feebly. There was foot drop bilaterally. All tendon reflexes were reduced or absent. The superficial reflexes were also less active than usual. The cremasteric reflex was brisk. The plantar responses were of flexor type. The muscles of the neck, trunk and extremities were flabby, weak and inadequately developed, but the general state of nutrition was satisfactory. The child weighed 11.7 Kg.

DYSTONIA MUSCULORUM DEFORMANS (TABLE 4)

CASE 10.—B. R., a Jewish girl aged 13 years, was admitted to the Bellevue Hospital [38] on April 17, 1933. At the age of 9 years (1929) twisting adventitious movements, involving the extremities and torso, had developed. These had

increased in severity, although there were occasional remissions, which lasted from a few days to three weeks. Frequently the movements were so severe that they kept the patient from sleeping. The past personal and family histories were irrelevant.

Examination showed that the patient was underdeveloped and undernourished and that there was generalized loss of subcutaneous fat. The extremities and torso were involved in more or less constant squirming and twisting movements, whereas the facial expression was fixed and exhibited no concern. During brief moments when the extremities were relaxed, the reflexes were brisk and equal on the two sides. There was hypertrophy of the sternocleidomastoid muscles, whereas the muscles of the extremities were small, but without obvious wasting. The patient weighed 43 Kg.

CASE 11.—J. W., a Jewish youth aged 17, a student entered the New York Hospital on Jan. 10, 1933, complaining of violent, uncontrolled body movements and deformity of the extremities. The onset of the illness had been gradual and was first noted at the age of 7. At that time there were plantar flexion and slight inversion of the left foot, with difficulty in walking. He became restless and was unable to relax or to stand and sit without movement. The right leg and foot were particularly affected. Sitting with the leg flexed on the abdomen gave maximum comfort. One year after the onset of the illness (1924) the thighs became so strongly adducted that urination was difficult unless the thighs were forcibly separated. Six months later dorsiflexion at the left wrist developed. At the end of the next five years (1928) there were no discrete purposeful movements without adventitious components. The family and past personal histories were noncontributory.

Examination revealed the movements described. The legs were "thin," but it was uncertain whether there was any muscular wasting. The muscles of the arms were strong, but sustained contractions seemed impossible. There were scoliosis, presumably from muscular atrophy, and only a small amount of subcutaneous fat. The patient weighed 40 Kg.

PARKINSON'S SYNDROME (TABLE 5)

CASE 12.—J. S., a Jewish clerk aged 40, entered the New York Hospital on Sept. 6, 1934, complaining of uncontrollable tremor. He had had influenza in 1918. In 1925 he first noted stiffness of the arms and legs. In 1930 tremor of the hands, arms, right leg and jaw became troublesome. At about the same time the face assumed a masked appearance, and there was excessive perspiration about the head. The salivary flow was excessive. The past and family histories were otherwise noncontributory.

Examination revealed that the patient was stooped and walked with small steps, holding himself rigidly. He had a fixed facial expression, and the skin of the face was covered with oily perspiration. The arms were carried in a semiflexed position. When he sat in a chair, when he walked or when the arms were not engaged in some definite movement through space, there was a coarse rhythmic tremor, which shook not only the arms but the entire torso. The tremor was continuous and disappeared only in sleep or after sedative medication. There was tremor in the legs also, particularly on the right side, which was more evident when the patient sat in a chair or when the legs were supported by the arm of the examiner. The resistance to passive stretch was generally increased. The patient weighed 58.6 Kg.

ENURESIS AND OTHER FACTORS IN NORMAL AND IN PSYCHOTIC PERSONS

A COMPARATIVE STUDY OF INCIDENCE AND INTERCORRELATIONS

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The present comparative study is concerned with the incidence and intercorrelations of enuresis and other factors in 475 normal children (previously reported [1]) and 224 psychotic subjects observed at the Boston Psychopathic Hospital.[2] To unify the material, for the adults only selected traits occurring in childhood were recorded.

MATERIAL

Diagnostically, of the 224 psychotic subjects 111 were schizophrenic and 46 had an affective psychosis (17 having the depressed, 18 the manic and 11 another form). As the remaining 67 subjects comprised series too small to be statistically significant, they were combined into one class which will be referred to herein as "the remainder." This group included 10 with a paranoid state, 12 with dementia paralytica, 18 with an undiagnosed psychosis, 17 with a schizoaffective disorder and 10 with miscellaneous diseases (2 with psychosis associated with other disease of the brain or nervous system, 1 with psychosis and mental deficiency, 3 with psychosis and psychopathic personality, 2 with psychoneurosis and 2 with psychopathic personality without psychosis). The ages ranged from 10 to 59 years, with the largest percentage (29) falling into the group between 20 and 24. There was a greater number of females (56.7 per cent), and 76.8 per cent of the patients were single.

As comparisons will be made with data on so-called normal persons differences in the nature of the material should be mentioned. The data on so-called normal subjects were derived entirely from children, and the information was obtained by examining and talking to the child and questioning one parent. The data on the psychotic material were obtained mostly by psychiatric social workers from

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From the Boston Psychopathic Hospital and the Neuropsychiatric Institute (formerly State Psychopathic Hospital) at the University of Michigan.

1. Michaels, J. J., and Goodman, S. E.: Incidence and Intercorrelations of Enuresis and Other Neuropathic Traits in So-Called Normal Children, Am. J. Orthopsychiat. **4**:79 (Jan.) 1934.

2. This group was originally described by K. M. Bowman (A Study of the Pre-Psychotic Personality in Certain Psychoses, A. Research Nerv. & Ment. Dis., Proc. **14**:180 [Dec.] 1933. The terminology and the methods of investigation are contained in that paper.

informants (members of the family, friends, employers and others) concerning patients admitted to the Boston Psychopathic Hospital, who were for the most part older than the control group of children. The ideal control data would have been obtained from a group of 224 adults of a distribution as to sex, age and other variables similar to that of the psychotic patients. Every possible means of securing reliable psychiatric data over a five year period was utilized by a large research group, consisting of social workers, psychiatrists and statisticians.[3] Doering and Raymond [4] have discussed the general reliability of psychiatric data.

INCIDENCE

There were among the normal children and the psychotic patients approximately the same proportion of foreign-born persons (table 1).

TABLE 1.—*Sex, Religion and Nativity of Subjects in Different Diagnostic Groups*

	Schizophrenia		Affective		Remainder		Total		Normal	
	No.	Per-centage	No.	Per-centage	No.	Per-centage	No.	Per-centage	No.	Per-centage
Age groups										
10-14	2	1.8	0	0.0	1	1.5	3	1.3	..	....
15-19	21	18.9	11	23.9	10	15.0	42	18.7	..	....
20-24	38	34.2	13	28.3	14	20.9	65	29.0	..	....
25-29	25	22.4	8	17.3	12	17.9	45	20.1	..	....
30-34	12	10.9	4	8.7	10	14.9	26	11.6	..	....
35-39	9	8.1	4	8.7	6	8.9	19	8.5	..	....
40-44	3	2.7	1	2.2	4	5.9	8	3.6	..	....
45-49	1	0.9	1	2.2	4	5.9	6	2.7	..	....
50-54	0	0.0	2	4.3	3	4.5	5	2.2	..	....
55-59	0	0.0	2	4.3	3	4.5	5	2.2	..	....
Sex										
Males	55	49.5	10	21.8	32	47.8	97	43.3	255	53.7
Females	56	50.5	36	78.2	35	52.2	127	56.7	220	46.3
Single	98	88.3	37	80.5	37	55.2	172	76.8	..	....
Jewish	13	11.7	5	10.8	10	14.9	28	12.5	184	39.0
Nativity										
Native born of native born parents	32	28.8	22	48.0	30	44.8	84	37.5	..	....
Native born of parents of mixed nativity (foreign or native)	70	63.0	19	41.3	27	41.8	116	51.9	..	....
Foreign born	9	8.1	5	10.8	10	14.9	24	10.7	42	8.8
Only child	2	1.8	1	2.2	2	2.9	5	2.2	90	19.2

In the psychotic group there were a lower percentage of Jews (12.5 per cent, contrasted with 39 per cent) and of only children (2.2 per cent contrasted with 19.2 per cent) than in the normal group. This low percentage of only children among the psychotic subjects tends to minimize the current opinion as to the precarious psychologic position of the "only child" in the matter of serious behavior and personality difficulties. As one might anticipate, the incidence of broken homes was higher for the psychotic group (table 2).

3. Schizophrenia, Statistical Studies from the Boston Psychopathic Hospital, 1925-1934.

4. Doering, C. R., and Raymond, A. F.: Reliability of Observation in Psychiatric and Related Characteristics, Am. J. Orthopsychiat. **4**:249 (April) 1934.

Neuropathic traits—thumb sucking, nail biting, impediments in speech and poor sleeping habits—were significantly less frequent among the psychotic subjects, whereas temper tantrums were reported in 29.5 per cent, as compared with 14.5 per cent in the normal persons, a notable difference, of 15 ± 3.3, with the affective group showing the highest incidence. In the psychotic patients nose picking, fatigue, nervous indigestion, fears, moodiness and delinquency appeared to be unusually rare. The occurrence of vasomotor disturbances in 16.5 per cent and

TABLE 2.—*Incidence of Neuropathic Traits and Other Factors*

	Schizophrenia		Affective		Remainder		Total		Normal	
	No.	Per-centage	No.	Per-centage	No.	Per-centage	No.	Per-centage	No.	Per-centage
Broken homes	49	44.1	14	30.5	24	28.0	87	38.8	140	29.4
Attachment to mother	25	22.4	10	21.8	9	13.4	44	19.6	..	....
Attachment to father	7	6.3	4	8.7	2	3.0	13	5.8	..	....
Attachment to both parents	0	0.0	1	2.2	3	4.5	4	1.8	..	....
Resentment of mother	1	0.9	1	2.2	0	0.0	2	0.9	..	....
Resentment of father	7	6.3	2	4.4	4	5.9	13	5.8	..	....
Resentment of both parents	1	0.9	0	0.0	0	0.0	1	0.4	..	....
Enuresis	21	18.9	9	19.5	10	14.9	40	17.9	108	24.7
Thumb sucking	5	4.5	2	4.4	6	8.9	13	5.8	106	25.5
Nail biting	25	22.4	12	26.2	11	16.4	48	21.4	226	51.3
Nose picking	9	8.1	1	2.2	2	3.0	12	5.4	..	....
Impediments of speech	9	8.1	4	8.7	4	6.0	17	7.6	85	20.0
Tantrums	26	23.4	17	37.0	23	34.4	66	29.5	61	14.5
Night terrors	22	19.8	13	28.3	12	17.9	47	20.9	..	....
Poor sleeping habits	1	0.9	1	2.2	1	1.5	3	1.3	82	19.1
Fears	13	11.7	3	6.5	4	6.0	20	8.9	194	45.0
Stubbornness	26	23.4	7	15.2	12	17.9	45	20.0	..	....
Moodiness	1	0.9	0	0.0	1	1.5	2	0.9	..	....
Obsessive phenomena	7	6.3	6	13.0	2	3.0	15	6.7	..	....
Emotional instability	19	17.1	7	15.2	6	8.9	32	14.3	..	....
Easy fatigability	1	0.9	0	0.0	0	0.0	1	0.5	..	....
Nervous indigestion	2	1.8	3	6.5	0	0.0	5	2.2	..	....
Food finickiness	32	28.8	10	21.8	18	26.9	60	26.8	..	....
Tics	4	3.6	3	6.5	1	1.5	8	3.6	..	....
Mannerisms	5	4.5	0	0.0	6	8.9	11	4.9	..	....
Delinquency	1	0.9	0	0.0	2	2.9	3	1.3	..	....
Constitutional physical anomalies	30	27.0	12	26.2	20	29.8	62	27.6	..	....
Constitutional mental anomalies	72	65.0	31	67.3	45	67.2	148	66.0	..	....
Physical disease	30	27.0	27	58.6	43	64.2	100	44.7	..	....
Endocrine disturbances	17	15.3	16	34.8	11	16.4	44	19.6	..	....
Vasomotor disturbances	26	23.4	3	6.5	8	11.9	37	16.5	..	....
Chorea	2	1.8	1	2.2	4	5.9	7	3.1	..	....
Convulsions	15	13.5	9	19.5	13	19.4	37	16.5	..	....
Masturbation	10	9.0	3	6.5	6	8.9	19	8.5	..	....
Perversion	10	9.0	4	8.7	1	1.5	15	6.7	..	....

of convulsions in 16.5 per cent contrasts with the findings of 60 per cent and 5 per cent, respectively, in an earlier study [5] of 80 neuropsychiatric patients. The percentage of constitutional physical and mental anomalies and of physical disease was high in the psychotic group.

When the emotional relationships of the patient to his family are considered, the incidence, aside from that of attachment to the mother (19.6 per cent), was strikingly low, especially in the sphere of resent-

5. Michaels, J. J., and Searle, O. M.: Calcium Content of the Cerebrospinal Fluid, Blood Serum and Serum Ultrafiltrate, Arch. Neurol. & Psychiat. **33**:330 (Feb.) 1935.

ments (0.9). In a control group referred to by Bowman [6] 11.7 per cent had a history of resentments. It is much more acceptable socially to admit attachments and even to foster them consciously than to bear resentments, which more often are consigned to the limbo of the unconscious. One might almost say that from a clinical standpoint—especially if the psychoanalytic view is taken—the opposite state of affairs is usually present; i. e., there are more resentments and less attachments. As suggestive evidence that the incidence of such factors as attachments and resentments was low in this material, the incidence is usually high in delinquent subjects, of whom Healy and Bronner,[7] found that 91 per cent had been extremely disturbed because of emotion-provoking relationships with others, mainly with others in the family. This situation was found in only 13 per cent of their sibling controls.

TABLE 3.—*Comparison of the Time of Cessation of Enuresis in the Subjects With a History of Persistent Enuresis and in All Subjects in the Normal and in the Psychotic Group*

	Age at Cessation, Years	Normal		Psychotic		Differences of Percentages
		Number	Percentage	Number	Percentage	
Enuretic	Before 8	68	63.0	15	42.9	−20.1 ± 10.3
	After 8	40	37.0	20	57.1	20.1 ± 10.3
Total	Before 8	68	15.5	15	6.9	− 8.6 ± 2.5
	After 8	40	9.1	20	9.1	0
Enuretic	Before 10	91	84.3	19	54.3	−30.0 ± 9.1
	After 10	17	15.7	16	45.7	30.0 ± 9.1
Total	Before 10	91	20.8	19	8.7	−12.0 ± 2.7
	After 10	17	3.9	16	7.3	3.4 ± 2.0

Of further significance is the high incidence of neuropathic traits in delinquent persons in contrast to their siblings.

As for the major thesis of this study, the incidence of enuresis, in our original paper [1] emphasis was placed on the clinical importance of persistent enuresis and its nature as an indicator of some form of "nervous instability." When the age of cessation was placed at 8 years, we found a difference in percentage of 20.1 ± 10.3 in subjects whose enuresis persisted beyond that point (table 3), the higher percentage being that of the psychotic subjects. When the age of cessation was placed at 10 years, the difference in the percentages became more notable. We present the material in another way: Ninety-one, or 84.3 per cent, of the enuretic children in the normal group (20.8 per cent of the total group of 437 for whom the time of cessation of enuresis was known) ceased enuresis before the age of 10 years, as compared with 19, or

6. Bowman, K. M.: A Study of the Pre-Psychotic Personality in Certain Psychoses, A. Research Nerv. & Ment. Dis., Proc. **14**:180 (Dec.) 1933.

7. Healy, W., and Bronner, A. F.: New Light on Delinquency and Its Treatment, New Haven, Yale University Press, 1936.

54.3 per cent, of the enuretic subjects in the psychotic group (8.7 per cent of the 219 psychotic persons on whom we had data), a conspicuous difference in percentage of 30 ± 9.1. It is interesting that Healy and Bronner [7] found that 22, or 21 per cent, of their 105 delinquent subjects were enuretic after the age of 8 years, as compared with 4, or 3.8 per cent, of 105 sibling controls, a substantial difference in percentage of 17.2 ± 4.3.

COMMENT

It has been a general presumption that the past histories of persons with psychoses manifest a high incidence of neurotic traits and other indicators of "nervous instability." The preceding findings, which do not corroborate these expectations, give rise to a few speculations. Is it possible to rely on a history as an accurate measure of events of a retrospective nature?

Is the low incidence of neurotic traits in the psychotic group a reflection of possible incomplete or inaccurate data, or does it represent a credible cross section? Certainly the relatively infrequent occurrence of these more passive and less obtrusive responses in psychotic persons, who react with more active and deeper conflicts, is striking in contrast to the higher frequency in normal and especially in neurotic persons, in whom such traits appear with facility. Is not this difference in response comparable to the cardiochronographic findings of Whitehorn and Richter, which, according to Cobb,[8] "indicate that the psychotic patient, although he may show superficial signs of emotion, may not show any significant change in the heart rate, whereas a psychoneurotic patient will have a great change of heart rate with emotion but may show little or no outward signs of this. . . . Schizophrenia and neurosis are unlike ways of reacting. The neurotic patient seems to overreact with his autonomic system, while the psychotic patient seems to have lost his ability to react adequately with this mechanism."

When an attempt is made to account for these apparently divergent results, an impasse is almost encountered. However, the incidence of the aforementioned traits and factors being much smaller in the psychotic group, it necessarily follows that correlations with enuresis are less likely to occur.

The present data in regard to intercorrelations do not seem to support our original thesis propounded for normal subjects. It must be kept in mind that statistical data are usually subject to a greater or less amount of error. From previous experience with psychiatric data we realize that there is sometimes a large degree of error, which would tend to reduce or even mask any true relationship between enuresis and

8. Cobb, S.: Review of Neurology and Psychiatry for 1935-1936, Arch. Int. Med. **58**:1111 (Dec.) 1936.

other related variables to zero—which is what we have observed in these data. However, zero correlation in these special data does not disprove the thesis that enuresis is a valuable clinical indicator of an ill balanced personality.

It will be interesting to compare the results of this study with a similar study of 1,000 patients at a psychopathic hospital which is soon to be released.

Although the conception gained from previous studies, that enuresis is an important indicator or individuation of an ill balanced personality, is still maintained by us, the present study does not seem to strengthen this idea. Temper tantrums appear to be a more prophetic indicator of the persons in whom psychoses are to develop. We might add that, aside from enuresis as an indicator of ill balanced personality and

TABLE 4.—*The Incidence of Enuresis and of Other Traits and Factors and the Associations of Enuresis with Other Traits and Factors in the Psychotic Subjects and in the So-Called Normal Children*

	Incidence, Percentage			Association with Enuresis, Percentage	
	Psychotic	Normal	Difference	Psychotic	Normal
Enuresis	17.9	24.7	— 6.8 ± 3.2		
Thumb sucking	5.8	25.5	—19.7 ± 2.6	5.6 ± 4.5	12 ± 5.2
Nail biting	21.4	51.3	—29.9 ± 3.6	3.8 ± 6.5	12 ± 4.0
Impediments of speech	7.6	20.0	—12.4 ± 2.7	—6.6 ± 8.2	17 ± 5.7
Temper tantrums	29.5	14.5	15.0 ± 3.5	—0.5 ± 5.4	14 ± 6.5
Poor sleeping habits	1.3	19.1	—17.8 ± 2.0	49.4 ± 17.6	5 ± 5.5
Fears	8.9	45.0	—36.1 ± 3.1	—8.6 ± 7.2	4 ± 4.2
Broken homes	38.8	29.4	9.4 ± 3.9	3.6 ± 5.3	10 ± 4.6
Jewish	12.5	39.0	—26.5 ± 3.1	—8.2 ± 10.7	—8 ± 4.1
Only child	2.2	19.2	—17.0 ± 2.1	2.2 ± 18.1	8 ± 5.5
Males	43.3	51.0	— 7.7 ± 4.1	15.8 ± 5.3	2.3 ± 4.2

especially of delinquency and temper tantrums as a historical indicator of psychosis, truancy was suggested in another study [9] as an indicator of psychopathic personality. It would be worth while to study these three indicators intensively from a clinical orientation to determine what clusters of traits tend to form about them and what constellations of traits seem to occur in association with them.

INTERCORRELATIONS

The classification used in the section on incidence has been preserved, and the presence or absence, with enuresis, of forty-one different traits and factors was determined.

In table 4 are listed ten items on which data were procured relative to both the normal and the psychotic subjects. It was found that the

9. Michaels, J. J., and Schilling, M. E.: An Attempt to Determine the Degree of Antisocial Behavior in Psychopathic Personalities and Its Correlation with the Porteus Maze and Binet-Simon Tests, Am. J. Orthopsychiat. **6**:397 (July) 1936.

incidence of most of the traits and factors, except enuresis, was significantly lower in the psychotic subjects, whereas temper tantrums were significantly more frequent in that group. The incidence of broken homes was also higher, but not to a statistically significant degree, in the psychotic group.

When these ten items were correlated with enuresis for the psychotic group—i. e., when their presence or absence with enuresis was determined—no marked trend toward association with enuresis was found. Poor sleeping habits were the one outstanding symptom significantly associated with enuresis among the psychotic patients. This was in marked contrast to the consistent trend toward association of enuresis with thumb sucking, nail biting, impediments in speech, and temper tantrums previously observed in the normal group. Impediments in speech in the normal children were found more likely to occur with enuresis than with any one or more of the other traits. This association did not exist at all in the psychotic group.

In addition to the ten items listed in table 4, the following 31 items were investigated for possible association with enuresis among the psychotic patients: Nativity (whether the patient was native born, of native or mixed parents, or whether he was foreign born); civil status; attachment to the mother, the father or both; resentment of the mother, the father or both; nose picking; night terrors; stubbornness; moodiness; obsessive phenomena; emotional instability; easy fatigability; nervous indigestion; finickiness about food; tics; mannerisms; delinquency; constitutional physical anomalies; constitutional mental anomalies; physical disease; endocrine disturbances; vasomotor disturbances; chorea; convulsions; masturbation, and perversion. When these factors were considered in each diagnostic group and for the group in toto, no statistical significance could be found in their presence or absence with enuresis.

CONCLUSIONS

1. The histories of 224 psychotic persons showed a significantly lower incidence of thumb sucking, nail biting, impediments in speech, poor sleeping habits and fears than did those of a group of 475 so-called normal children.

2. These psychotic persons showed a significantly higher incidence of temper tantrums than a group of so-called normal children.

3. The incidence of enuresis and of broken homes did not present any significant, marked difference in the two groups.

4. The low incidence of nose picking, moodiness, easy fatigability, delinquency, resentments and vasomotor disturbances in this group of psychotic patients was striking.

5. The persistence of enuresis after the age of 10 years was significantly more frequent in the psychotic patients (whether considered only in those who had enuresis past 3 years of age or in the entire group) than in the so-called normal children.

6. In the group of 224 psychotic subjects there was no tendency to positive correlation between enuresis and the presence or absence of forty-one various traits and factors, or between it and any particular type of psychosis.

Dr. Carl R. Doering, of the School of Public Health, Harvard University, gave advice in regard to the statistical analysis of the data.

CEREBRAL IMPALUDATION

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In 1932, in a note presented at the Académie de Médecine, I gave the name "cerebral impaludation" to a method which I have employed since 1927 in the treatment of dementia paralytica. This method consists of injecting into the interior of the encephalon a few cubic centimeters of blood containing the malaria organism. This is only one chapter of what I have called "intracerebral therapeutics," therapeutics characterized essentially by the injection of remedies (in the largest sense) into the white substance of the brain.

I conceived this method in the hope of breaking down the encephalolymphatic barrier which opposes the penetration of therapeutic agents into the nerve centers; I have used it since 1925 without success in this respect, however, in the treatment of several patients in my department, especially those with dementia praecox.

Before these experiments, I had tried, with the aid of a steel wire passed through a needle introduced beforehand into the brain, to make notches in the white substance and thus to permit medicaments injected into the blood or the muscles to penetrate into the cerebral mass. Analysis of the cerebrospinal fluid showed that the substances did penetrate, at least in the majority of cases, but the method did not seem worth introducing into current practice because the notch in the brain closes rapidly, and the barrier is restored.

These experiments are not dangerous. I have not encountered a fatal result, or even a serious accident to a patient.

I have adopted the method of cerebral injection of malaria organisms in the treatment of patients with dementia paralytica in my department because these persons, for the most part, have reached a final stage of the disease and with them malarial therapy, as developed by Wagner-von Jauregg and applied universally, would fail regularly. On the basis of statistics from a department similar to mine, it seems that good results, although generally incomplete, are obtained by the classic method of impaludation in not more than 13 per cent of patients and that 18 per cent die. However, I repeat, these unsatisfactory figures concern patients who were severely affected and had been treated without success by various methods.

I have carried out the intracerebral therapy of dementia paralytica for ten years. I considered it necessary to wait for ten years before

I reported on a method the effects of which can be appreciated only retrospectively. Prolonged observation alone can tell whether relapses will occur with frequency and whether accidents of more or less severity will not annihilate the immediate advantages of the therapeutic method.

My house residents, however, have published several articles on the subject. Coulloudon [1] made use of the material for the preparation of his thesis; Ferdière [2] reported on 10 patients recovered from dementia paralytica, and Chavastelon,[3] after studying the records of my patients, summarized statistically the results of my ten years' work.

TECHNICAL PROCEDURE

In 1932, in an introduction to the thesis by Coulloudon, I read a short note at the Académie de Médecine, on a method of cerebral impaludation by which an injection of Plasmodium vivax was made into the white substance or the ventricles of the brain of patients with dementia paralytica.

After a few trials, the frontal lobes were chosen for the injections. Other lobes may be used, but do not seem to be as tolerant; their use sometimes causes disturbances and seems not to give as good results.

Since 1932 I have discontinued injections into the ventricles; the procedure is of doubtful therapeutic value, is often followed by painful sensations and is sometimes even dangerous. It is possible that the ventricles received too large doses of blood—from 10 to 12 cc. Smaller injections were without inconvenience, but also without result.

On the other hand, I added tetanus antitoxin to the blood which was injected into the brain in the hope that this antitoxin, which, as Roux showed, neutralizes many other toxins, would act on the toxins produced by the spirochete and aid the action of the cerebral trauma and the virulent blood.

This proved to be true; the mixture of malaria blood and antitoxin acted more rapidly and more severely than the blood alone.

It would be desirable to possess a serum in which there was a stronger neurotropic antitoxin than that of tetanus; possibly one will be discovered; I have tried anticobra serum, which does not show any particular advantage.

Intracerebral therapy of dementia paralytica (the name "cerebral impaludation" may be retained) consists at present of injecting into

1. Coulloudon, J.: Contribution to the Study of Treatment of Dementia Paralytica: Cerebral Impaludation, Paris, E. Le François, 1932.

2. Ferdière, G.: Intra-Cerebral Therapeutics of Dementia Paralytica, Bull. Soc. path. exot. **26**:830, 1933.

3. Chavastelon, A.: Intracerebral Therapeutics of Dementia Paralytica: Cerebral Impaludation, Technic and Results, Paris, Vigot Frères, 1936.

one frontal lobe, or into the two lobes at the same time, from 3 to 5 cc. of a mixture of equal parts of malaria blood and tetanus antitoxin.

I used first a serum containing 3,000 units, obtained from the Institut Pasteur. Lately I have used 20,000 units or 10,000 units of the purified serum.

The technic of the operation is simple; it has been described minutely by Chavastelon; if one uses an electric trephine, the procedure is completed in a few minutes.

CLINICAL COURSE

The harmlessness of cerebral injection is absolute. The patient feels no shock. One can say that he does not perceive the operation, although he is not asleep. The injection does not in the least modify the pulse, the blood pressure, the reflexes or the vascular reflection of the retina. It does not give rise to sensations of dizziness or to gastric disturbances; on the whole it produces no painful symptoms.

Immediately after the operation the patient may return to his occupation and may undertake a long journey by car or train on the same day.

The constituents of the blood are not modified, and in the days following the operation the composition of the urine remains as before; appetite and sleep are not disturbed.

In the cerebrospinal fluid there is often an increase in the number of lymphocytes, but the period of lymphocytosis is brief.

A few hours after the injection one may observe a rise in the temperature of from 1 to 1.5 degrees C. (1.8 to 2.7 degrees F.); on the next day the temperature is normal.

Injections may be repeated after a few days or a few months. In consideration of Besredka's production of anaphylactic shock by injections into the brain of guinea pigs, one might fear serious accidents in man. There have been none. Repetition of injections of virulent blood, therapeutic serums or antitoxins into the brain of patients with dementia paralytica has thus far caused no disastrous reactions. I insist on the remarkable innocuousness of the injection of blood containing antitoxins into nerve centers because at the beginning of my experiments, and perhaps even today, this practice has been taxed as dangerous; however, it was known only by hearsay.

In a group of 550 patients with dementia paralytica treated by cerebral impaludation, 1 death was reported; this was evidently a coincidence. It has happened several times that patients with this disease have died on the eve of a day fixed for operation, and others as they were being taken to the operating room. I can, in justice, take no notice of this single death, and I continue to insist on the innocuousness of cerebral injection.

There might be apprehension concerning the occurrence of late accidents when nerve fibers are cut and capillaries opened; by these routes, an infection which is not indifferent when inoculated into the blood might conceivably be conveyed directly into the nerve centers.

The possibility of formation of a scar, more or less irritable, might also inspire apprehension for the patient's future. Ten years of experience has judged the validity of these fears; there have not been observed in patients with disease of long standing any symptoms of cerebral abscess, ictus, convulsions or paralysis. Epileptiform manifestations, which are not unknown after peripheral impaludation, have not appeared after cerebral impaludation.

The evolution of paludism when the organisms are injected into the brain may be divided into two phases: the one, silent; the other, febrile —one might say, a cerebral and a peripheral phase, with the reservation that the development of the second phase is not substituted for, but is associated with, the evolution of the first phase.

Fever appears between the fifth and the twelfth day, generally on the seventh or eighth day. The temperature rises frequently to 41 C. (105.8 F.). The attacks may be of several types. Coulloudon reported on this in the work previously cited, to which the reader is referred for details.

Apyretic evolution was frequent at the beginning of my experience. In these patients, I nearly always found *schizontes* in small numbers in the blood; the therapeutic results, however, did not differ much from those obtained in patients with high fever. During the last few years an apyretic course has disappeared, perhaps as a result of the admixture of the blood with antitoxin, perhaps because the stock now maintained in the department for twelve years has been passed through hundreds of patients and has acquired a high degree of virulence.

The fever is interrupted by the administration of 6 Gm. of quinine sulfate during eight days—sometimes after the fourth or fifth paroxysm, sometimes after the tenth, or even the eighteenth. I have thus studied the action of this form of pyretotherapy; variations in the number of attacks and the duration of the febrile cycle, however, have not seemed to influence greatly the clinical or the humoral results. Although in cerebral paludism at least fever has an important role, it does not carry with it the whole effectiveness of the treatment. Paludism following cerebral injection is mild and without accident or complication. When the fever ends (often spontaneously), I rarely use chemotherapy. As a test of the intrinsic value of the method, no treatment consecutive to cerebral impaludation was administered between 1927 and 1932; yet I have known of no relapse. Since 1932 I have treated with drugs several patients in whom the reactions of the cerebrospinal fluid remained positive; it is universally considered, although I am not cer-

tain, that this practice is necessary. However, as the period is short during which the method has been used, the question is still unsolved.

Wassermann reactions of the blood rapidly become negative in a small number of cases; they nearly always become more normal. Lymphocytosis is modified, as is the reaction of Guillain. I have been able, however, to make only a small number of examinations of the cerebrospinal fluid in series; these few observations seem to establish that the fluid becomes normal immediately and that this evolution is only slightly influenced by chemotherapy, even when intensive. When the Wassermann reaction of the blood remains positive after the procedure, an effort is made to reduce it, and this is easily accomplished.

The duration of the treatment, that is, the time that elapses between the cerebral impaludation and the discharge of the patient from the hospital, is variable; it is often short; many patients are discharged two months after the inoculation. This speedy discharge is advantageous to the patient, over whom the hospital life, painful and monotonous, exercises a highly pernicious influence.

PROGNOSIS

What are the results of cerebral impaludation in the treatment of dementia paralytica? After the patients on whom observations were reported by Coulloudon and Ferdière and those to whom treatment was administered outside the hospital were omitted, Chavastelon compiled the results for 435 patients with dementia paralytica treated in my department from the beginning of 1927 to October 1936. Three hundred and fifty-three (81.14 per cent) were cured; 12.87 per cent failed to improve, and 26 (5.97 per cent) died from intercurrent diseases or accidents several months or years after the operation. In round numbers, treatment with cerebral impaludation of institutionalized patients with dementia paralytica, among whom, however, Chavastelon erroneously included several extramural patients, resulted in success in 80 per cent and in failure in 20 per cent.

Two other statistical statements emphasize the severity of the disease in patients whom I have treated. If the patients with dementia paralytica who enter the institution at Villejuif are not treated with cerebral impaludation, 73 per cent die during the first six months, and 88 per cent, in the first year.

Of the 353 patients with dementia paralytica who were considered to be cured after the operation, "269 had been submitted to impaludation, acetarsone therapy or diverse medication, and, of this number, 237 had been in institutions for malarial treatment, in hospitals for mental disease or in nursing homes."

Patients who are less affected, with the disease in an early stage, or who are treated at home benefit, as is easily understood, more from

cerebral impaludation; they recover with certainty, though it is true that the same patients when treated with simple impaludation also recover in from 90 to 95 per cent of cases.

The meaning of the term "cured" should be discussed as it is applied to patients with dementia paralytica to whom treatment has been given by the method I have described; it may be thought that though the patients improve they are still defective intellectually and are more or less incapable of social adjustment. This criticism is not valid, at least for the great majority of my patients; far from being outclassed and defective in psychic power, their status appears to be superior to that before the disease. I know of many who have risen several degrees in the social scale and have been able to accomplish work which needed initiative and intellectual adaptability of which they would not have been capable before the disease. I may cite a few examples.

A traveler for a grocery firm became subdirector of an important bank. A lawyer, after recovery, became head of the bar in an important prefecture. A rural proprietor, who had been indolent before, made his land prosper by daring initiative. The works of an authoress became greatly appreciated and more original. A clerk at the prefecture of the Seine was placed in a hospital for mental disease with a six month leave of absence, to be followed by a pension for "incurable dementia paralytica"; he left the hospital two months after cerebral impaludation and was examined by a commission of physicians in his administration, who gave him back his former position and canceled the proposal for a pension; some time later he secured a post superior to the one he had and has filled it to the satisfaction of his superiors; he has become the father of a healthy child and has remained in the best of health, without any treatment, for the past five years.

There are many examples of patients with dementia paralytica of long standing whose activity and sureness of intelligence have grown in a way evident to every one.

Parallel to this, physical recovery, a veritable rejuvenation, is observed; many patients become vigorous athletes, active and untiring. Virility, which had been absent for several months or years before the operation is resumed rapidly. The concept that persons treated with paludism are mental defectives who must be restricted to automatic activity is inept if applied to those treated by the cerebral route.

These favorable results are frequent, and even the rule. In addition, I consider that a patient with dementia paralytica is cured who conforms to conditions established at my clinic as a "social test." One may legitimately speak of cure when the patient is (1) considered as normal by those around him; (2) restored without anxiety to the family circle; (3) socially rehabilitated, i. e., when he resumes his previous occupation or adapts himself to work necessitating equal or superior initiative; (4) judged by his physician to have regained his normal state; (5) restored to sexual activity; (6) in good physical health, and (7) free from relapse for several years.

The question of relapse remains for precise definition. It was mainly for this reason that I considered it prudent to wait ten years before publishing the results of intracerebral therapy. Unfortunately, despite my efforts, many patients have failed to continue to report, and I do not know what has become of them. Chavastelon reported observations on only 7 patients who returned to the department; the findings show that a recurrence of dementia paralytica was doubtful; some patients, however, may have been admitted to, and died in, other institutions. I have been able to follow about 200 of the patients, none of whom has had a relapse.

Relapses are in all probability rare, certainly rarer than after treatment with ordinary impaludation. With the latter method, approximately one half of the patients are again committed to an institution about two years after discharge.

Rare also, if they exist, are the transformations of dementia paralytica into what are called psychotic forms or paranoid syndromes; if a few cases have been observed, it has always been possible to find in the antecedents of the patient signs of a psychosis on which the meningoencephalitis was engrafted.

ANATOMIC CONSIDERATION OF THE EFFECTS

How does cerebral impaludation act? Can one deduce plausible hypotheses from anatomic observations? Postmortem examinations on patients who had been recently treated are lacking, but examinations of organs of animals show that cerebral injection dilates the capillaries and spreads and cuts nerve fibers. The gap thus formed tends to heal after the first few hours from the afflux of leukocytes, on the one hand, and from energetic proliferation of neuroglia cells, on the other; this proliferation takes place, however, at a certain distance from the lesion.

At the same time one sees, not only around and near the gap but in parts of the brain much farther away, an accumulation of microglia cells, of which the abundance and variety of shapes indicate intense activity; they penetrate between cells, surround the vessels and seem to converge toward the operative wound, although this orientation is not evident in all preparations.

Healing of the cerebral wound is the work of neuroglia cells; if the section examined is made soon after the inoculation, one notices at the site of the injection proliferation of neuroglia cells without new formed vessels and without any other modification of the nerve elements.

A year after the operation it is difficult, if not impossible, to find traces of the lesion; one is directed toward the region to be examined by the opening in the skull, which is more or less filled with bone, and by the perforation of the dura mater, which remains visible for a long

time; microscopic examination, however, does not aid one in finding any alteration in the cerebral substance; the scar has disappeared, and nothing indicates the site of the lesion made by the injection.

This complete restitution of the nerve tissue permits one, as Chevastelon said, to understand the remarkable absence of late accidents, of which I have spoken.

Cerebral injection into animals of colored liquids or china ink enables one to follow, when the experiment is well made, the passage of the liquids through the nerve centers; they can be followed often to a great distance—on the one hand, into the spaces around the cells and, on the other, into those around the capillaries; some of the liquid enters the capillaries; some passes along the vessels toward the subarachnoid space, and some is fixed by microglia elements. This transfer of visible liquid injected into the white matter was suspected long ago; one knew, for example, that an injection of tetanus antitoxin (Roux and Borrel, 1898) made anywhere into the brain of an animal immunizes rapidly all nerve centers.

These observations lead one to believe that cerebral impaludation in patients with dementia paralytica acts through several processes, the efficiency of which is additive and becomes stronger as it increases. First, even if cerebral injection does not produce shock, in the usual sense, it is no less true that it stimulates and makes more active the neuroglia and the microglia cells. If the former are not motile and proliferate only as the most rapid process in repair of the operative wound—to which it is not certain that their action is limited—the activation of microglia cells is more important. Bruetsch noted that if, under the influence of induced malaria, the entire reticuloendothelial system becomes activated, microglia cells, being overcome, as it were, by the toxins of the spirochetes, remain inert. "The absence of activity of the microglia cells seems to be a reason that there has been failure to check the paralytic process even with malaria therapy." Cerebral injection reactivates the microglia cells not only in the neighborhood of the wound but in all centers; according to the view of Bruetsch, which is probably correct, resumption of this activity is necessary for the therapeutic action of paludism.

Although experiments on animals are not of great assistance, one can well believe that antitetanus serum, in neutralizing, in part at least, the toxins of the spirochete that "stupefy" the microglia, assist in activating and mobilizing the full potency of this tissue. This energetic activation of microglia, the most important phagocytic element of the brain, is evidently of great utility in cleaning up the centers and removing the spirochetes and their toxins and the various waste products of the cells.

A few units of tetanus antitoxin may be of little value; it was for that reason that I substituted for the serum containing 3,000 units serums with from 10,000 to 20,000 units. Theoretically, they are preferable. Theoretically, also, anatoxin should show greater activity. I am conducting experiments with this substance; I cannot yet report any results, though its injection into the centers, even in doses used for injection into the skin, is without danger.

ACTION OF THE MALARIAL ORGANISM

The preceding observations, suggested by anatomic experiments, do not concern the virus of malaria when inoculated into the brain.

Does P. vivax when introduced into the nerve centers pass immediately into the vessels and act as if it had been inoculated under the skin?

On the other hand, does it become modified in the interior of the nerve tissue; does it take on an unknown form and stay there, or does it circulate? Does it exercise a direct and special action on the centers? It is not easy to answer these questions.

A few days after the operation, almost without exception, P. vivax multiplies in the surrounding blood, and paludism develops, as after the classic inoculation. This does not justify setting aside the possibility of the silent evolution of cerebral paludism during the preceding days.

Ascione and Mariotti expressed the belief that the parasite can be transformed into a filtrable virus; although the investigations of Marchoux, Troisier and others have not confirmed the existence of an ultramicroscopic form of the parasite, it is reasonable to believe that the malarial organism, as customarily observed, may undergo changes which may have, as Orticoni stated, on the basis of my experience, "a more characteristic action on the agent which causes dementia paralytica."

However, even if P. vivax when inoculated into the brain gives rise only to paludism in all points similar to that produced by subcutaneous inoculation, one must not, for that reason, doubt the clinical results secured with the cerebral method and discard it immediately.

It is evident that the process, still unknown, by which malaria acts in dementia paralytica possesses more force, rapidity and efficiency in a brain prepared by cerebral injection, as a result of which neuroglia and microglia cells, when impregnated with tetanus antitoxin, are activated. These cells have already been changed and rendered more receptive for a few days, when fever and all that paludism involves suddenly become operative.

If one wishes to assert the identity of cerebral impaludation and the method of impaludation introduced by Wagner-von Jauregg, one

must admit that in the case of the former, paludism acts on a brain that has been prepared, having already undergone modifications which assist the effect of the paludism and probably make it doubly efficient.

These are possibly trifling considerations; only clinical results count. As one does not yet know how the malarial organism acts when inoculated into the blood, it is daring to try to understand the action, certainly more complex, when it is inoculated into the brain. It is probable that everything is in favor of a beneficial action: stimulation and activation of the brain tissues, on the one hand, and malaria, on the other; perhaps other unknown, even unsuspected, qualities play a major role.

CONCLUSION

In spite of the unknown factors, intracerebral therapy, by its innocuousness, its ease of application and the excellent results which it has given in patients with dementia paralytica, merits a consideration which it will probably be accorded when it is better known.

EUNUCHOIDISM

A PSYCHIATRIC AND ENDOCRINE STUDY OF SIX CASES

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AND
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The great advance in knowledge of hormones, especially the "sex hormones," made in the past ten years has led to renewed interest in the problem of the relation of the endocrine glands to personality and to mental disorders. In the past it had been claimed, on the one hand, that there is a close etiologic relationship between the endocrine glands and mental disorders and, on the other, that no such relationship exists. Recent reports in the literature on the use of androgens and estrogens in the treatment of endocrine and psychiatric disorders and quantitative studies on the excretion of these substances in the urine by patients presenting various psychiatric and endocrine syndromes have led us to make an investigation of the problem in eunuchoidism.

Eunuchoidism is a syndrome characterized by hypoplasia of the testes and accessory genitalia, deficiency in secondary sex characters, delay in fusion of the epiphyses of the long bones and a tendency to elongation of the extremities, but no considerable impairment of health. The first sharp delimitation and thorough description of this clinical picture were made by Tandler and Grosz,[1] although there had been previous reports of such cases. Since Tandler and Grosz published their findings, many studies of the condition have been recorded. Many of these were reports of individual cases. Most of them dealt mainly with the physical aspects or with pathologic investigations. Relatively few dealt with the psychologic picture. It is not our intention here to review the literature. This has been done in articles by various authors: Sterling,[2] Fischer,[3]

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From the Division of Psychiatry (Dr. Carmichael) and the Department of Medicine (Dr. Kenyon), the University of Chicago.

1. Tandler, J., and Grosz, S.: Ueber den Einfluss der Kastration auf den Organismus, Arch. f. Entwcklngsmechn. d. Organ. **29**:290-324, 1910.

2. Sterling, W.: L'état mental des eunuchoïdes, Rev. neurol. **30**:492-499, 1923.

3. Fischer, H.: Psychopathologie des Eunuchoidismus und dessen Beziehungen zur Epilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **50**:11-48, 1919.

Fraenkel,[4] Krisch,[5] Falta,[6] Climenko and Strauss,[7] Schlund,[8] Peritz,[9] Altmann,[10] Löwenthal,[11] Onuf [12] and Garfunkel.[13]

Eunuchoidism is to be differentiated from eunuchism, infantilism, hypophysial dystrophia adiposogenitalis and late eunuchoidism. This has been done by Falta.[6] Some authors do not follow this differentiation but consider eunuchoidism as a form of infantilism and include late eunuchoidism and hypophysial dystrophia adiposogenitalis under eunuchoidism. Cryptorchidism is frequently present in eunuchoids, but is not always associated with eunuchoidism. Histologic studies made post mortem have regularly revealed degenerative and hypoplastic changes in the gonads but no characteristic changes in the other endocrine glands. Löwenthal [11] and Altmann [10] recently published the results of such studies.

There is disagreement as to the type of personality, the intelligence and the psychopathologic symptoms associated with eunuchoidism. Some authors, e. g., Krisch [5] and Sterling,[2] have claimed that there is a characteristic psychologic picture, while others, e. g., Fraenkel [4] and Löwenthal,[11] asserted that such a picture does not exist. The intelligence has been said to be normal by many authors; others have spoken of the high incidence of feeblemindedness. Epilepsy has been described as common, and the similarity to the so-called epileptic character has been stressed by Fischer.[3]

We made a clinical study of 6 eunuchoids from the physical, endocrine and psychiatric points of view, with emphasis on the last in this report. In addition, estimations of the urinary excretion of androgenic

4. Fraenkel, F.: Der psychopathologische Formenreichtum der Eunuchoiden, Ztschr. f. d. ges. Neurol. u. Psychiat. **80**:560-574, 1922-1923.

5. Krisch, H.: Die psychischen Erscheinungen der Eunuchoiden, Ztschr. f. d. ges. Neurol. u. Psychiat. **45**:136-161, 1919.

6. Falta, W.: Endocrine Diseases, ed. 3, translated by M. Meyers, Philadelphia, P. Blakiston's Son & Co., 1923.

7. Climenko, H., and Strauss, I.: Eunuchoidism, Arch. Neurol. & Psychiat. **1**:726-748 (June) 1919.

8. Schlund, F.: Beitrag zur Psychopathologie des Eunuchoidismus, Monatschr. f. Psychiat. u. Neurol. **53**:323-342, 1923.

9. Peritz, G.: Ueber das psychische und soziale Verhalten der Eunuchoiden, Arch. f. Frauenk. u. Eugenik **14**:13-28, 1928.

10. Altmann, F.: Ueber Eunuchoidismus, Virchows Arch. f. path. Anat. **276**: 455-547, 1930.

11. Löwenthal, K.: Der Eunuchoidismus des Mannes, Beitr. z. path. Anat. u. z. allg. Path. **86**:426-439, 1931.

12. Onuf, B.: Study of Eunuchoidismus in Its Various Aspects Bearing on Other Pathological States, Am. J. Dermat. & Genito-Urin. Dis. **16**:459, 517 and 590, 1912.

13. Garfunkel, B.: Ueber Eunuchoidismus und die Heterosexualität der sekundären Geschlechtsmerkmale, Schweiz. med. Wchnschr. **44**:500-506, 1924.

and estrogenic substances were made[14] and extracts of the urine of pregnant women administered, in attempts at therapy. The results are given in the form of individual case reports.

REPORT OF CASES

CASE 1.—A. B. (referred by Dr. I. Becker), an insurance clerk, aged 30, unmarried, was first seen at the University of Chicago Clinics in August 1933 and has been under our care since.

History.—Except that the maternal grandmother died of carcinoma and a maternal aunt of hypertension, nothing was known regarding the grandparents, aunts and uncles. The patient's father, an Austrian Jewish tailor, who came to the United States in 1905, died at the age of 52, of asthma. He was ambitious, strict and cautious and supported his family well. The mother, aged 55, was "nervous" and mildly diabetic and worried excessively; she managed the family after the father's death. She was said to have been more lenient with the children than was the father. There were 7 siblings, the patient being the fourth, with 3 older brothers and 2 sisters and 1 brother younger than himself; none of the siblings was married. One of the older brothers was shiftless and was known as "the black sheep of the family." The mother and 7 siblings lived together and got along without difficulty, but had little to do with one another outside the home.

The patient was born in Austria on Aug. 16, 1906. Birth and early development were normal. He came to the United States when 2½ years of age. He had no serious illnesses except acute nephritis, without sequelae, at the age of 12. He worked well at school, where he obtained high grades and got along well with his schoolmates. He did not participate in athletics because of his small stature, but took part in social activities and was assistant editor of the high school paper. He took a commercial course (at the suggestion of his father, who thought he would not be able to learn a trade) and graduated at the age of 18. He began work at the age of 16 as a clerk in a wholesale glassware and chinaware company and left after a year. Then, for three months he was an errand boy in a bank, but left because he did not like the work and did not want his friends to see him running errands. For the next thirteen years he worked as clerk for two companies and reached a maximum salary of $90 a month. He associated well with fellow employees, liked the part of his work which dealt with underwriting and the selling of insurance after office hours, disliked the map work required of him and was successful until April 1935, when on transfer to another department he began to feel insecure. At this time there developed aching in the eyes and elsewhere in the body, and he had to take sedatives to secure relief. His dissatisfaction with the filing he had to do, the conviction that he was fitted for more responsible duties, the realization that there was little or no chance for advancement and his dislike of the department head led him to protest to the manager. As member and vice president of two clubs, where most of the members were younger than he, he was busy in the evenings, had to do a certain amount of public speaking (of which

14. (*a*) Gallagher, T. F.; Peterson, D. H.; Dorfman, R. I.; Kenyon, A. T., and Koch, F. C.: The Daily Urinary Excretion of Estrogenic and Androgenic Substances by Normal Men and Women, J. Clin. Investigation **16**:695-703, 1937. (*b*) Kenyon, A. T.; Gallagher, T. F.; Peterson, D. H.; Dorfman, R. I., and Koch, F. C.: The Urinary Excretion of Androgenic and Estrogenic Substances: Studies in Hypogonadism, Gynecomastia and Virilism, ibid. **16**:705-717, 1937.

he had always been fearful) and was the leader, owing to his show of initiative. His social activities were limited to club duties and to time spent with friends who had been his fellow members in another organization several years previously. Formerly he had attended the movies twice a week. He went to the theater occasionally, read a good deal of both fiction and nonfiction and disliked love stories and western and mystery fiction. Although he avoided parties (since he was likely to be asked how old he was because of his youthful appearance) and was shy on meeting new people, he expressed his opinions freely to persons whom he knew well. He did not see much of friends of his own age, since most of them were married or engaged. He found his physical appearance a handicap, felt that he would be more successful if he looked older and considered himself in the position of watching others grow up and pass him by. He was aware of such tendencies in himself as worrying over trifles, difficulty in delegating responsibility in club work, preference for doing things himself, concern over doing or saying the wrong thing and over what others think of him and lack of self confidence.

Psychosexual History.—The patient did not recall any curiosity about sex or indulgence in sex play or masturbation during childhood or adolescence. During adolescence erections without sexual desire were present. He had never had intercourse. He mixed equally well with both sexes and felt at ease with both. He had more men than women friends. He had never had a "girl friend."

Present Illness.—Until the age of 21 he did not realize that there was anything wrong with him and thought that there would be normal development as time went on. At 23 he began to worry about the lack of sexual development, but at first was too shy to go to a physician. He wrote a letter to a newspaper medical columnist and was advised to consult a physician who specialized in endocrine disorders. He received treatment for six months, but discontinued it because of the expense. After a few months he began to worry about his condition again. He considered it a handicap which made it more difficult for him to get ahead in the world, felt insecure, worried about losing his job and not being able to get another, felt set apart from other people and thought that his contemporaries and persons younger than himself were passing him by in business. At times he became depressed and melancholy and found his mind dwelling on his sexual condition to the exclusion of other things. He never discussed it with any one—relatives or friends. Another physician was consulted when he was 25. For the first time his condition was fully explained to him, and he was advised that probably he would never be cured completely and that it would take years to achieve anything. At this time he was willing to do anything possible to help himself and had hopes that something could be done for him as new advances in knowledge of the hormones were made. He was under treatment for one year, at first with an extract of the anterior lobe of the pituitary (antuitrin), without results, and then with a preparation of a gonadotropic substance from the urine of pregnant women (antuitrin-S), with the appearance of a slight growth of pubic hair. Treatment was abandoned because of the expense. In August 1933 he was referred to the University of Chicago Clinics.

Examination (fig. 1).—When first seen the patient was 26 years of age and 5 feet and 4 inches (163 cm.) in height, he weighed 111 pounds (50.3 Kg.) and appeared much younger than his years. The sitting height was 80.7 cm. (ratio of sitting to standing height, 49.4 per cent), and the span, 172 cm. (ratio of span to stature, 105.5 per cent). His father, mother and 7 brothers and sisters were all under 5 feet and 5 inches (165 cm.) in height; 1 brother was excessively heavy (height, 5 feet and 2 inches [157.5 cm.] and weight, 160 pounds [72.6 Kg.]), but

there was no known genital defect among them. The patient had had mumps at the age of 8 or 9 years, but orchitis was not known to have occurred. The voice was high pitched, and the laryngeal prominence was absent. The testes, lying normally in the scrotum, measured 2.7 by 1.7 by 1.3 cm.; the epididymides were small, and the prostate was barely palpable. The penis was 4.7 cm. long. Erections occurred occasionally and seminal discharge not at all. There were a small amount of hair at the root of the penis, a few strands of axillary hair and just enough lanuginous facial fuzz to require shaving once in three weeks. Hair on the limbs was scant. There was no special abnormality in distribution of fat.

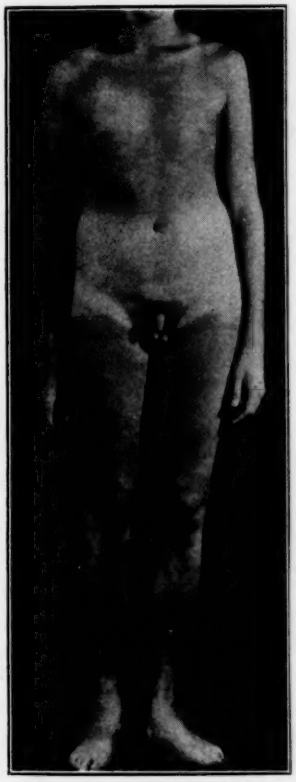

Fig. 1 (case 1).— A. B.

The Wassermann and Kahn reactions of the blood serum were negative. Examinations of the urine and blood showed nothing abnormal. Roentgenograms showed a small, enclosed type of sella turcica, which was not regarded as pathologic. There was moderate general constriction of the visual fields for form. The basal metabolic rate ranged from —12 to —23 (Mayo Foundation standards). From 60 to 320 mg. of creatine was present in several twenty-four hour specimens of urine when the patient was on a conventional diet. Fusion of the epiphyses of the head of the humerus, the tip of the acromion, the bases of the metacarpal bones and the proximal two rows of the phalanges had not taken place—a delay of from three to five years beyond normal. The epiphyses about the elbow were completely

fused; those at the knee, incompletely so, and those at the lower end of the radius and ulna were still open. A dextrose tolerance test showed normal values. Immature rats and rabbits given injections of the urine exhibited none of the gonadotropic effects produced by that of the castrated animal. The urine contained 15 international units of androgens per day when hydrolyzed fifteen minutes before extraction and estrogenic substance equivalent to 2 micrograms of estrone (theelin) per day.

Diagnosis.—The diagnosis was hypogonadism, involving all functions of the testis, the etiologic factor being unknown.

Clinical Course.—During three and a half years of observation certain progressive changes have appeared, amounting to a substantial advance of puberty. Some of this progress has probably been due to vigorous treatment, although this is not at present subject to rigorous proof. The influence of extract of bull testis and of androstanediol on this patient was recorded by Koch.[15] By January 1936 the prostate could be palpated as two pea-sized lobes, and ejaculations of small amounts of albuminous material occurred. There were no other changes. From January 17 to October 16 the patient received a total of 535 cc. of an extract containing the gonadotropic substance from the urine of pregnant women (antuitrin-S),[16] 100 rat units per cubic centimeter, taking 3 cc. six days a week during the last six months of therapy. After one month of this treatment erections increased in frequency, as they had with bull testis extract and androstanediol. The ejaculation increased in amount, and sexual excitability was heightened. After three months the prostate and testes seemed larger; the penis measured 7.4 cm. in length, and fine hair appeared on the upper lip. After four months the patient needed to shave twice a week in order to keep a smooth skin, and an acneiform eruption appeared on the face. After six months his voice had broken in so striking a manner that his friends and acquaintances commented on it. Interest in women was enhanced. By eight months the two prostatic lobes exceeded hazelnuts in size; the first nocturnal emission occurred, and on one occasion an emission appeared when he was in the company of a girl. At this time he was greatly pleased with the changes in himself, said that he no longer associated as much with persons younger than himself, and told of having more friends, of being less willing to continue at his work and of planning to resign in order to take up the study of a profession he would like, e. g., pharmacy or law. While he hoped that the changes would be permanent, he realized that his wishes for a change might to some degree be responsible for them. At the end of nine months' treatment he was shaving twice weekly; the pubic hair had substantially increased (fig. 2); the penis measured from 6.9 to 7.7 cm. in length; the deep pitch of the voice was well sustained; the testes, now 3.3 by 2 by 1.8 cm., were larger, and the ejaculation was more abundant and thicker, but still contained no sperm. Curiously, motile sperm, in from one to four or five high power fields, were first observed on December 17, two months after the cessation of treatment and are still present in the same number. Four months after the last injection, there has been little or no recession in the signs of puberty, except perhaps a slight decline in sexual desire. In general, no tangible constitutional effects were produced by the extract of the urine of pregnancy. The basal metabolic rate, however, now ranges from —5 to —9 rather than from —15 to —23, as it did in the year before treatment.

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15. Koch, F. C.: Biochemistry and Physiological Significance of the Male Sex Hormones, J. Urol. **35**:382-398, 1936.

16. Dr. E. A. Sharp, of Parke, Davis & Company, supplied us with antuitrin-S. Dr. I. Becker made most of the injections.

CASE 2.—C. D., an American waiter and college student, aged 26, of mixed English, Irish and German stock, unmarried, was first seen at the University of Chicago Clinics in October 1934.

History.—Both grandfathers were patients in hospitals for mental disease for a short while before they died, at an advanced age. Two uncles were alcoholic, and a third died in a hospital for mental disease. One grandmother, an uncle and an aunt died of pulmonary tuberculosis. The other grandmother died of carcinoma, and an aunt had one breast amputated. The patient's father, a railroad engineer aged 56, had a quick temper and was said to have caused many quarrels with his wife during early married life by his drinking. Although away from home a great deal at his work, he owned his own home and several smaller pieces of property; he always provided well for the family. While he turned his wages over to his wife and left her to manage the financial affairs of the family, he resented this

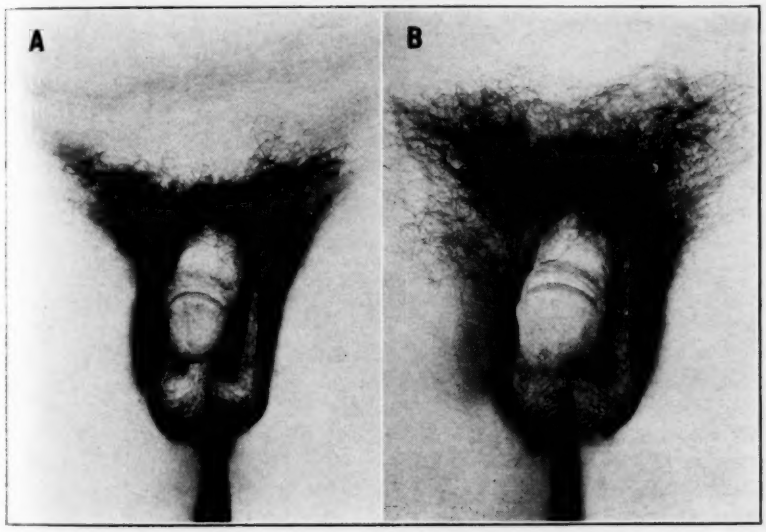

Fig. 2 (case 1).—External genitalia (*A*) before treatment and (*B*) after treatment with an extract of the urine of pregnant women.

and the domination of his wife. He did not appear to know how to behave toward his children, of whom he was fond, and preferred his daughters to the patient. He was disappointed that the patient was not a girl, always had an attitude of mistrust of the boy's ability and whipped him as late as at the age of 18. The patient felt that he had never become acquainted with his father, who was like a stranger to him, and regretted that they had no confidential talks, as he felt father and son should have. The patient's mother, aged 54, was healthy until the birth of twin girls in 1914, since when she had been in poor health. She was sensitiye, irritable, stubborn, insistent on her own way, overcleanly about the home, too strict with her children, whom she managed poorly, and successful in managing the family's affairs, though she deprived herself of things she needed. She preferred the patient, when a child, to the other children. There were 4 siblings, the patient being the second, with an older sister and 2 younger twin sisters. One of the latter married to escape the discord at home. The others, who were unmarried, lived at home. Neither the father nor the mother appeared to realize the possible

effect on the children of their attitudes and the discord in the home. The children were not permitted to play with other children, and young men were not permitted to visit the girls at home.

The patient was born in Kentucky on Aug. 25, 1910. He was cyanotic and almost died at birth and was not strong as a small child, but little is known of the early development except that walking was delayed until he was almost 3 years of age. He sucked his thumb as a small boy and had enuresis and night terrors until the age of 10 or 11. He still bit his finger nails. As a baby he probably slept with his parents. He slept with his older sister until he was 5 or 6, and then in the same room with his sisters until he was given his own room at the age of 12. He was very ill with whooping cough before the age of 4 years. At 10 he suffered concussion when struck on the head with a box, and when 12 or 13 he had poison oak dermatitis, with swelling of the scrotum. No other serious illnesses occurred. He was an average student and at 15 graduated from the ninth grade. He returned at the age of 16 for a business course of one year; at present he is attending the first year of college, with plans to enter the priesthood if possible. He did not participate as he wished in the activities of his schoolmates, because of the demands on his time by his parents and their refusal to permit free association with other children, even at home. He resented being compelled to assist with the housework and had no happy recollections of childhood. In his early teens he had to deliver newspapers after school. At the age of 15 he worked for six months as a clerk in a hardware store, but left to return to school, during which he also worked as a laborer in a tobacco factory. At 16 he worked in a chain store organization and during the following two and a half years was promoted several times, with accompanying increases in salary, until he was receiving $18 a week, as assistant manager. To leave home and increase the opportunities for advancement, he requested and was given a transfer to another town as assistant manager at a salary of $22.50 a week, but he resigned after only four months because of sensitiveness about his physical condition. For the next six years he worked in three large cities, as a theater usher, a window dresser, a waiter and a bus boy, but never again earned as much as he had when assistant manager of a chain store. He associated well with employers and bosses, but at times had difficulties with fellow employees. He was ambitious, overfastidious, perfectionistic, quiet and reserved, sensitive about his physical inferiority and irritable if opposed when he was right, had few interests outside his work and was religious. Though brought up as a Presbyterian, he joined the Roman Catholic Church in 1935 (at the same time as his parents and sisters) because he had previously lost his interest in living, wanted to do something worth while and felt he could achieve this as a priest.

Psychosexual History.—The first information on sex was gained from other boys at school when the patient was 10 or 11 years old. At this time there was mutual exhibitionism with other boys; masturbation was also learned, but was not practiced much and was abandoned at 14, when he was told it was harmful. Erections were common, but there were no nocturnal emissions and no ejaculation with masturbation. During late adolescence he indulged with pleasure in kissing and fondling girls, but was afraid to go further because of his physical condition; he had never had sexual intercourse. There were no homosexual experiences, although he had been called homosexual because of his appearance. Since the age of 19, he had avoided contacts with girls and women as much as he could, but had enjoyed the friendship of both men and women. He wanted a home and children, in spite of his experiences at home.

Present Illness.—He first became vaguely aware of his sexual underdevelopment at the age of 10 or 12, when his playmates commented on the difference between their genitalia and his. At 14 he became acutely aware of his condition and began to feel inferior and ashamed. He left school to go to work at 15 because he was teased about his defect by other boys. Between 17 and 19 he went around with girls and could not understand why girls seemed to like him so much. When he was 18, a man friend told a girl with whom the patient was friendly about the patient's physical condition. The patient was much upset by this and began to feel that every one was making remarks about him. This, coupled with difficulties at home and lack of respect from subordinates at the store, made him decide to leave town. He felt more and more dissatisfied and unhappy when, on leaving home, he found the situation even more intolerable. People began to impose on him because of his youthful appearance; his earning power was affected, and he withdrew more and more from contacts with other people. For a short time he lived with another young man, but during most of the time he lived alone. When girls asked to be taken out he always made excuses. About the end of 1930 he decided there was no chance for him to get ahead and became depressed; he contemplated suicide, but was afraid to carry it out. In 1932 he went to a hospital about his condition. The physician who saw him laughed about his condition and made fun of him. He consulted a second physician, but could not afford the high fees that were asked. In June 1934 he went to a clinic in Chicago and was referred for treatment to the University of Chicago Clinics, to which he came in October 1934.

Examination (fig. 3).—The patient was 24 years of age and 5 feet and 10 inches (177.8 cm.) in height; he weighed 152 pounds (68.9 Kg.) and had a youthful appearance. The sitting height was 89.3 cm. (ratio of sitting to standing height, 50.2 per cent), and the span, 192 cm. (ratio of span to stature, 108.5 per cent). The voice was somewhat high in pitch and tired easily; the laryngeal prominence was absent. The thyroid gland was diffusely enlarged to a moderate degree. The normally placed testes were small, measuring 2.2 by 1.4 by 1.1 cm.; the epididymides were small, and the prostate was hardly detectable. The penis varied from 3.8 to 5.9 cm. in length. Erections occurred occasionally; seminal discharge, never. There was a small amount of pubic and axillary hair, but no facial hair or hair on the limbs. The hips, thighs and legs were relatively adipose, giving a feminine contour to the lower half of the body, but there was no special accumulation of fat over the pubic region or in the breasts.

The Wassermann and Kahn reactions of the blood serum were negative. A low grade hypochromic anemia was present, with 4,030,000 red cells per cubic millimeter; the percentage of hemoglobin was 80 (calculated from oxygen capacity). The urine was normal. Roentgenograms of the sella turcica were normal. There was slight general constriction of the visual fields for form. The basal metabolic rate ranged from —6 to —15 (Mayo Foundation standards). From 158 to 970 mg. of creatine was present in twenty-four hour specimens of urine when the patient was on a conventional diet. Fusion of the epiphyses of the head and the median epicondyle of the humerus, of the olecranon and of the proximal end of the radius was incomplete. The epiphyses at the distal ends of the radius and ulna and those of the metacarpal bones and the phalanges were open; the epiphyses at the distal end of the femur and the proximal ends of the tibia and fibula were incompletely fused. The delay was from four to five years beyond normal. A dextrose tolerance test showed a low value of 33 mg. of dextrose per hundred cubic centimeters of blood in the second hour after administration of 72 Gm. of dextrose, but otherwise nothing abnormal. The urine showed no gonadotropic properties when injected into a rabbit or when a concentrate obtained by alcoholic

precipitation was injected into immature rats. The urine contained 28 international units of androgens per day by the method of hydrolysis for fifteen minutes. Hydrolyzed urine contained on an average the equivalent of 2 micrograms of estrone per twenty-four hour specimen.

Diagnosis.—The diagnosis was hypogonadism, involving all functions of the testes, the etiologic factor being unknown.

Clinical Course.—The patient was treated with androstanediol in the summer of 1935, and the results have been reported by Koch.[15] An extract containing the gonadotropic substance from the urine of pregnant women (antuitrin-S), 100

Fig. 3 (case 2).—C. D.

rat units per cubic centimeter, was given between Jan. 11 and July 14, 1936. In all, the patient received 291 cc. By the end of treatment the penis was from about 6.2 to 6.8 cm. long; there was possibly an increase in prostatic tissue, and erections were considerably augmented; these results, however, are to be regarded as negligible. There was no substantial change in the size of the testes or in the secondary sex characters.

Case 3.—E. F. (referred by Dr. M. Kolovros), a Greek dishwasher aged 30, unmarried, was first seen at the University of Chicago Clinics in August 1935.

History.—The only information obtained about his grandparents, aunts or uncles was that the maternal grandparents died when over 100 years old, that an uncle

died of "paralysis" and that all 10 maternal aunts and uncles were excitable. The patient's father, a farmer, died at 65, of disease of the kidney, when the patient was 5 years of age. He associated well with people, was quiet, dominated his household and was kind to the children, who were fond of him. He was away from home for two or three years at a time, when he worked in a bakery at Istanbul, Turkey. The patient's mother, aged 70, who is now ill with pelvic carcinoma, assumed direction of the family after her husband's death; she would become angry if the children did not do things to her satisfaction. However, the children liked her; the patient was fond of her. There were 6 siblings, of whom the patient was the youngest, with 3 married brothers and 1 single and 1 married sister. The siblings associated well together. As the youngest, the patient had received more attention than the others and saw little of the older siblings because of the great difference in age. At present, the patient is living with an older brother.

The patient was born in Greece on April 23, 1906. Birth and early development were normal, and breast feeding was continued for from one and a half to two years, which is said to be the usual practice in Greece. Until the age of 5 or 6, he went to sleep in his mother's arms each night and slept with his parents until he was 7, after which he slept alone in a separate room. The only siblings at home with him were the immediately older brother and sister. To enable his parents to work without interruption, he was sent to school at the age of from 3½ to 4 years, but formal schooling did not begin until the age of 6. He reached the equivalent of the eighth grade at the age of 12, being an average student and adjusting well with teachers and schoolmates. Until the end of his fourth year at school boys and girls were together, but in the fifth and sixth years he attended a boys' school in a nearby town. He learned to speak English after coming to the United States, at the age of 13. He attended school for fourteen months, beginning in the fifth grade and reaching grade 7 B. No serious illnesses occurred except "kidney trouble," at the age of 5 or 6. His first job in the United States, as a heater in a bolt works at $14 a week, was given up after six months because of the heat and a rash on his hands. He left his second job as a messenger in a steel mill because his earnings were small, owing to frequent closing of the mill. From then, he worked in restaurants as waiter, dishwasher, assistant cook and counterman, earning from $10 to $14 a week and frequently leaving a job to take a vacation for a month or longer. He was out of work for one and a half years in 1931 and 1932. He liked his work, but was not able to do heavy work and left several jobs when he felt he was working too hard or when the bosses angered him. He was quiet as a child and enjoyed playing with other children. As an adult, he was shy, self conscious, very sensitive, serious minded and given to worry over trifles and had a feeling of guilt if he inadvertently insulted some one. He associated mostly with friends of his own age and sex who were conservative and knew more than he did, and he disliked persons who talked foolishly. He enjoyed playing cards, reading and walking; he read Greek fiction and poetry and English magazines and newspapers, e. g., "True Story Magazine" and "Hollywood Revue," attended the movies twice a week and liked to go to lectures and debates. He liked to do odd jobs about the house, such as gardening and carpenter work. As a boy he went to church regularly, and for the first two or three years in the United States he continued this; after that he lost interest in religion. He did not care about money and wanted only enough to enable him to go home to Greece to visit his mother.

Psychosexual History.—Masturbation was learned from other boys at the age of 11 or 12; there was pleasure but no ejaculation, and the practice was discontinued after the age of 12 or 13, when an older brother threatened that he might

die as a result. He had always had erections and experienced nocturnal sexual dreams twice a month, but without emission. He had only very slight sexual desire and had had no other sexual experiences.

Present Illness.—He first became aware of the difference between himself and other boys at the age of 15 or 16; he consulted a physician, who gave him injections, without results, and told him that he would become fat when he reached 25. He was worried about his condition but, except for several examinations in 1927, did nothing about it until January 1935. At that time he consulted a physician,

Fig. 4 (case 3).—E. F.

who explained the condition to him and said no treatment was possible except grafting of "monkey glands." He had always felt badly about his difference from other men, although it had not led him to avoid people or to associate with younger men. No one but the physicians whom he consulted knew about his condition. People tended to mistake him for a man much younger than he was, and he found his youthful appearance a decided handicap in securing good work and pay, since employers took his appearance as an excuse for not paying him full adult wages and gave him a boy's rather than a man's work. At first he resented this, but he became accustomed to it. He learned to be quiet and not to talk about himself and his youthful appearance. In August 1935 he decided to seek further treatment and advice and came to the University of Chicago Clinics.

Examination (fig. 4).—The patient was 29 years of age and 5 feet and 9 inches (175.2 cm.) tall, weighed 113 pounds (51.3 Kg.) and possessed the long arms and legs of the classic eunuchoid condition. The sitting height was 83 cm. (ratio of sitting to the standing height, 47.8 per cent), and the span was 190.5 cm. (ratio of span to the stature, 108.7 per cent). The voice was somewhat high in pitch, and the laryngeal prominence was small. The normally placed testes measured 2.2 by 1.5 by 1.4 cm.; the epididymides were small, and the prostate could barely be felt. The penis was 4.2 cm. long. Erections occurred occasionally, but there had been no seminal emissions. A small amount of axillary and pubic hair was present, but there was no hair on the limbs and no facial hair. The patient was excessively lean, and there were no local accumulations of fat.

The Wassermann and Kahn reactions of the blood serum were negative. Examinations of the blood and urine as a routine showed nothing abnormal. Roentgenograms of the sella turcica were normal. The visual fields for form and color were normal. The basal metabolic rate ranged from —6 to —14 (Mayo Foundation standards). From 160 to 360 mg. of creatine was found in twenty-four hour specimens of urine. Fusion of the epiphyses of the head of the humerus, of the distal ends of the radius and ulna, of the lower end of the femur and of the proximal ends of the tibia and fibula was still incomplete. The epiphyses about the elbow were fused. There, thus, was a delay of about five years. A dextrose tolerance test gave normal results. The Friedman test and injection of urine concentrates into immature female rats indicated no detectable increase in the excretion of gonadotropic substances. The urine contained 7 international units of androgen per day according to the method of hydrolysis for fifteen minutes, and the equivalent of 1 microgram of estrone.

Diagnosis.—The diagnosis was hypogonadism, involving all functions of the testes, of unknown cause.

Clinical Course.—From Jan. 10 to July 6, 1936, the patient received 346 cc. of a preparation containing a gonadotropic principle from the urine of pregnant women (antuitrin-S), 100 rat units per cubic centimeter,[17] and 3.5 cc. daily during the last three months of the treatment. The penis seemed to enlarge, measuring 8.2 cm. at the end of treatment; the prostate, however, did not change, and no ejaculations occurred. The testes were possibly slightly larger, being 2.6 by 1.8 by 1.3 cm. at the end of the treatment. Secondary sex characters were unaltered. After five months of treatment a small, tender button of breast tissue appeared under the right nipple. These results are to be considered negligible.

Case 4.—G. H., a bookkeeper and law student, aged 23, unmarried, was first seen at the University of Chicago Clinics in February 1935.

History.—There were no significant facts concerning the grandparents, aunts and uncles. Of the children of the maternal aunts and uncles, 1 had a mental illness, 1 received special treatment for blindness and 1 suffered from hemophilia. The patient's father, aged 50, was born in Latvia. He made a fair living by operating a grocery store and meat market, and was described as good hearted, not energetic, seldom angry, indifferent to his religion and ambitious for his children to succeed. He shared the responsibility of the home with his wife. The patient's mother, aged 45, worked at home and went out of her way to help other people. She had full charge of the children's training when they were small, showed no preferences for any of them and was ambitious for them to succeed in life. She followed orthodox Jewish customs fairly closely. The patient liked his father, but

17. Dr. M. Kolovros, Gary, Ind., made most of the injections.

preferred his mother. One brother, aged 18, was taller than the patient, had a pleasing personality, was popular and lazy and planned to attend college. He and the patient had the usual childish squabbles, but associate well now. Both were sent to a Jewish school until the age of 13; since, they have followed their own way in religion.

The patient was born in Chicago on Nov. 30, 1912. Birth and early development were normal. He graduated from high school at the age of 17, with an average grade of 87 per cent, and then took a prelegal course in college for two and a half years. Two years in a law school, with failure in one subject in the second year, due to spending too much time on extracurricular activities, led to withdrawal of the family support. Six months later he entered an evening school and completed one of the two years of study required for graduation. As a boy he worked in the family store. He worked in a law office as part of his training in law. During 1935 he worked as a bookkeeper and stenographer for $15 a week, but left when his wages were not increased. From the age of 9 to 14 he had a fear of fire, as a result of a scare at 9, when a house four doors away was burned. He always made friends readily and until he went to high school participated in all the activities at school and in the neighborhood. He attended the Young Men's Christian Association and belonged to the Boy Scouts until the age of 12 or 13; he also took piano lessons, at his mother's insistence. At high school he shunned athletic activities because of his physical condition, but belonged to the band, was on the debating team and participated in other clubs. At college he was active in fraternity work and in the band.

Present Illness.—Even as a small boy he was aware of having undescended testes, as his mother took him to a physician for advice about the condition when he was 7. He gave up Y. M. C. A. activities at 12 because other boys ridiculed him. At this time he began to worry constantly about his condition, was upset when the penis did not grow and pubic hair failed to develop and was pleased when the family moved to a new neighborhood, where the boys knew nothing of him. At 15 he requested his parents to take him to a physician. He was treated with a glandular preparation for four or five months; at the age of 16 a unilateral operation was performed, at which the testis was brought down. Another exploratory operation was performed when he was 21.

He had had erections and nocturnal sexual dreams without emission but had never masturbated. When at college he met a girl two years younger than himself and for four years kept company with her. For two years they had intercourse, with mutual orgasm, but with no ejaculation by the patient. The girl knew of his physical condition and had agreed to marry him. It was she who advised him to come to the University of Chicago Clinics. She lost interest in him when she went to another college and learned of the difference between the patient and normal men. Although upset by this, the patient decided it was the girl's right, since he could not satisfy her passionate nature. Since, he had been lonely. He had been much bothered by his youthful appearance, as many persons remarked on it, though he had hidden his actual condition from his friends. He had become resigned to his condition as untreatable and felt that it would not be fair to a woman to marry her. He found it difficult to meet girls, since they looked on him as too young, but felt he would like to meet them on an intellectual basis.

Examination (fig. 5).—When first seen at the University of Chicago Clinics in February 1935, he was 22 years of age and 5 feet and 7 inches (170 cm.) tall and weighed 149 pounds (67.6 Kg.). The sitting height was 86.5 cm. (ratio of sitting to standing height, 50.8 per cent), and the span, 181.3 cm. (ratio of span to the stature, 106.6 per cent). The voice was fairly normal, and the laryngeal

prominence was absent. The thyroid showed slightly diffuse enlargement. The prostate gland could not be felt, and the scrotum was small and empty. The penis measured 3.5 cm. in length. Erections were frequent, but seminal discharge had not occurred. There was a small amount of axillary and pubic hair, but shaving had never been required. He was plump generally, with slight local accumulations of fat over the pubis and under the breasts.

The Wassermann and Kahn reactions of the blood serum were negative. Examinations of the blood and urine gave normal results. Roentgenograms of the sella turcica were normal. The visual fields were normal for form. The basal

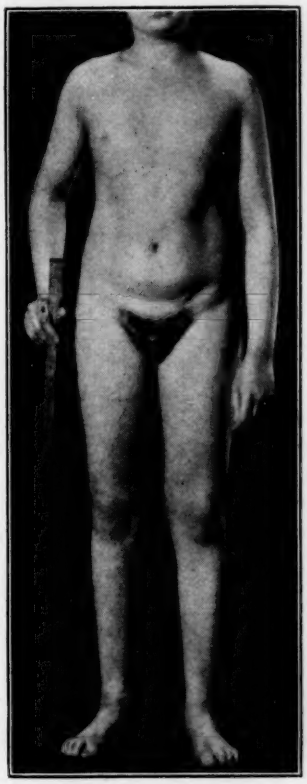

Fig. 5 (case 4).—G. H.

metabolic rate ranged from —5 to —17 (Mayo Foundation standards). No significant creatinuria was found in the one specimen examined. The epiphyses of the head of the humerus, the distal ends of the radius and ulna, the distal end of the femur, the proximal end of the tibia and fibula and the head of the radius were open. The epiphyses of the media, epicondyle of the humerus, the acromion, the metacarpal bones and the phalanges were partially closed. The delay in closure, which was especially marked in the elbow and the hand, was two years beyond the normal. A dextrose tolerance test showed a curve characteristic of mild diabetes. The patient excreted 18 international units of androgen per day, the urine being hydrolyzed fifteen minutes before extraction. The equivalent of 2 micrograms of estrone was excreted per day.

CASE 5.—I. J. (referred by Dr. Henry Schmitz), a truck driver and musician, aged 21, unmarried, was first seen at the University of Chicago Clinics in May 1936.

History.—There was nothing of significance concerning the grandparents, uncles and aunts. The patient's father, aged 56, a music teacher, who came to the United States from Sicily in 1903, was described as generous, even tempered, quiet, not energetic and always thinking of new compositions in music. He was a good musician, was fond of his children and had taught each of them to play a musical instrument. He made no objection to his wife's domination of the home. The patient's mother, aged 56, was energetic and generous, had a bad temper, was ambitious for the children to succeed and was strict about their performing their religious duties. There were 9 siblings, the patient being the seventh, with 4 older sisters and 2 brothers and 2 younger sisters. The oldest sister had had a "nervous breakdown" with convulsive movements four years before and now had carcinoma of the uterus. The oldest brother died in infancy, of convulsions. Another sister was irritable and "nervous." The patient adjusted well with all the siblings, except for arguments with the brother and the immediately younger sister. The family lived in New York for six months when the patient was a baby and in a small town in Michigan for a year when he was about 9.

The patient was born in Chicago on April 9, 1916. His mother suffered from attacks of dizziness and falling during the pregnancy, but birth and early development were normal. Breast feeding continued for almost two years. Enuresis began in childhood and persisted, and now occurred about once every three or four months. Until the age of 9 or 10 he slept in a room with his younger sisters; after this he had a room of his own. He was always on the honor roll in grade school, from which he was graduated at the age of 15. He left technical high school after six months to go to work, as he did not like school. He associated well with schoolmates and teachers, participated in all activities and at times led the group. Since the age of 16, he had worked as a truck driver, musician and clerk and at odd jobs, his maximum wages being $14 a week. He was energetic and conscientious, made friends readily, enjoyed tennis, riding, the movies, the theater, dancing and reading, performed his religious duties only at Easter and was not shy.

Present Illness (including psychosexual history).—The patient had erections and attempted intercourse with a girl of his own age at the age of 9 or 10. About this time he first became aware of his lack of sexual development and asked his father about it. He was taken to a physician at the age of 12, and a laparotomy was performed, at which something is said to have been done to help him. He became definitely interested in sex at 12, when he discussed it with other boys. There was no masturbation, but nocturnal sexual dreams occurred, without emission. When he was 12 and began to put on weight, people began to regard him as 15 or 16. At 13 he had sexual relations with a girl of his own age, having an orgasm but no ejaculation. At 14 or 15 he repeated the act with the same girl, but felt unsuccessful and made no more attempts, although he continued to think about girls and intercourse and indulged in kissing. He did not concern himself much about his condition until the age of about 15 or 16, when he became sensitive about the size of his genitalia and the remarks of other boys. When 16 or 17 he had a girl friend for a year, but gave her up as he felt he had no right to have a girl friend because of his physical condition. The girl did not wish to break with him. Since, he has taken girls out occasionally. When 17 or 18 he discussed his condition with his parents and consulted several physi-

cians, who told him that he could not be helped, that he would be all right or that a long course of treatment might help. He received injections of a preparation containing a gonadotropic substance from the urine of pregnant women (antuitrin-S) for six months, in 1935 and 1936. During this period he tried masturbation for the first time and experienced pleasure and orgasm without ejaculation, but he has not tried it since. Because of his appearance, he was regarded as a boy of 15 or 16, though he was treated as a person of 20. He was resigned to the fact that adult male characteristics had not developed and tended to accept his situation calmly. His parents, particularly his mother,

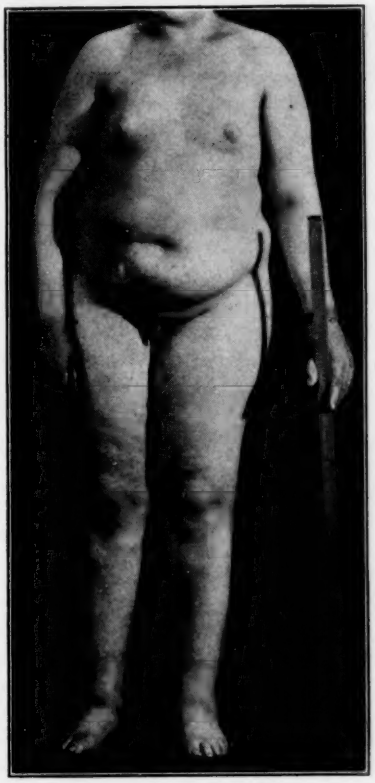

Fig. 6 (case 5).—I. J.

were much more concerned than he about the matter of marriage and carrying on the family name. In the past year he had gained over 30 pounds (13.6 Kg.). He was referred to the University of Chicago Clinics in May 1936.

Examination (fig. 6).—The patient was 20 years of age, was 5 feet and 7 inches (170 cm.) tall and weighed 193 pounds (87.5 Kg.). The sitting height was 85 cm. (ratio of sitting to the standing height, 50 per cent), and the span, 172.5 cm. (ratio of span to stature, 101.4 per cent). Neither testis could be palpated. The voice was somewhat high in pitch. The penis was 3.5 cm. long, and the prostate could not be felt. There were a small amount of pubic hair at the root of the penis and little axillary hair. A few strands of hair were present on the upper lip, but he had never shaved. He was grossly obese, and the fat was

distributed generally, including the breasts, abdomen and pubic region, but these areas could not be regarded as disproportionately adipose.

The Wassermann and Kahn reactions of the blood serum were negative. Examinations of the blood and urine made as a routine showed nothing abnormal. The sella turcica was normal. Visual fields for form were undisturbed. The basal metabolic rate was —18 (Mayo Foundation standards). The epiphyses about the elbow had closed. Those about the shoulder were still open. The epiphyses of the distal ends of the radius and ulna were open; those of the heads of the metacarpal bones were still incompletely closed, but that at the base of the first metacarpal bone was closed. Fusion was beginning in the epiphyses about the knee. There was thus no substantial delay. The dextrose tolerance curve was flat. The patient excreted an average of 17 international units of androgens per twenty-four hours, the urine being hydrolyzed fifteen minutes before extraction, and the equivalent of 7 micrograms of estrone per day.

CASE 6.—K. L., aged 36, an American of Irish-English-Scotch stock, married, professional, was first seen at the University of Chicago Clinics in September 1936. There was nothing of significance concerning the grandparents, uncles and aunts. The patient's father, aged 76, a successful Methodist minister, was wrapped up in his work and was very strict, especially in regard to religious observances; he dominated the home and arranged the training of the children, but was amiable and loving. Although the patient was attached to him, he avoided arguments and took his problems to his mother by preference. The patient's mother, aged 73, who had taught at a small college before marriage, was described as lovable, active in church affairs and less strict than the father. The children were all more attached to her than to the father. There were 6 siblings, the patient being the second, with an older sister and a younger brother and sister who were living and married and a brother and sister who died at birth. The brother who was living had one undescended testis, was closer to the father than were the other siblings and used to quarrel with the patient. The family always lived in small towns, on a minister's salary. All 4 siblings were college graduates.

The patient was born in Ohio on July 24, 1900. Birth and early development were normal; he was a fat baby. Enuresis was present until the age of 9 or 10 years. There were no serious illnesses. At school he had to work hard at his studies. He took a premedical course at college, but decided to study osteopathy so as to ensure a living; he graduated in osteopathy in 1925. From the age of 11 he worked at odd jobs, and when at college had to work to supplement the allowance his father sent him. When 15 the habit of pulling out his eyebrows developed and has persisted. He was active as a small boy and participated in extracurricular activities at school. At college he was popular and a fraternity member, went out with girls, took part in athletics, though he was considered too small and light, and belonged to the glee club. He had always been interested in hunting and guns, in photography and cameras and in traveling. He played bridge, hunted and fished, was active in fraternal and social organizations, taught in Sunday school and went to church regularly. He knew his wife, a college classmate, for four years before marriage, in 1925, and has adjusted well with her. They adopted twin girls in 1927. Since graduation, he has practiced successfully in a small town.

Present Illness (including psychosexual history).—As a young boy he was aware of having undescended testes, but hoped they would descend. He did not become acutely aware of his difference from others till he was 14, when his

father took him to the family physician, who recommended an operation. At the operation one testis was observed to be completely undescended and the other at the inguinal ring; there was postoperative infection, and the testes ascended again. At high school he avoided swimming because of sensitiveness about his condition; he worried about it, although he was not teased or ridiculed. At 14 he masturbated with other boys and had orgasm without ejaculation; he later abandoned the practice. He had kissed and fondled girls and had erections and sexual desire. Before marriage he discussed his condition with his wife. He had intercourse regularly and had orgasm without ejaculation; his wife also achieved orgasm. Although he discussed his physical condition with physicians, he tended to hide it, and always anticipated comments about it. He came to the University of Chicago Clinics in September 1936 for advice and treatment, without too great expectation of good results but eager to cooperate.

Examination.—When first seen, he was 36 years of age and 5 feet and 11 inches (180.3 cm.) tall and weighed 172½ pounds (78.2 Kg.). The sitting height was 91.1 cm. (ratio of sitting to standing height, 50.5 per cent), and the span 198.7 cm. (ratio of span to stature, 110.2 per cent). At the age of 21 he grew 4 inches (10 cm.). The voice was somewhat high in pitch, and the laryngeal prominence was absent. The penis was 3.8 cm. long, the scrotal sac small and empty and the prostate impalpable. There was a small amount of hair in the pubic area and in the axillas, with enough fuzz on the face to call for shaving every two or three weeks. There were no special local accumulations of fat.

The Wassermann and Kahn reactions of the blood serum were negative. The sella turcica was unusual in shape, but not clearly pathologic. Visual fields for form were normal. The basal metabolic rate was —21. The patient had mild hypochromic anemia, the hemoglobin being 81 per cent (Newcomer) and the red blood cells 4,200,000. The lines of the epiphyses at the proximal end of the humerus, the distal ends of the radius and ulna, the proximal end of the tibia and fibula and the distal end of the femur were still distinct. A dextrose tolerance test showed a flat curve. The patient excreted an average of 33 international units of androgens per day, the urine being hydrolyzed fifteen minutes before extraction.

COMMENT

In none of the eunuchoid persons studied was the etiologic factor in the condition clear, nor was it known whether the gonads or the pituitary body was primarily at fault. It is to be recalled that a similar uncertainty usually prevailed after the best autopsy studies thus far available (Altmann,[10] Löwenthal [11]). In each instance the development of the secondary sex characters was that of the normal boy aged from 12 to 15. The basal metabolic rate ranged from —6 to —23 and was usually within the lower limits of normal. Creatinuria, a metabolic characteristic of childhood, was present in 3 patients. Dextrose tolerance curves varied from flat to a form suggestive of mild diabetes. The patients were thin, fat or of ordinary build; special localizations of deposits of fat about the hips, pubic region and mammae were sometimes present, but were not always as definite as is commonly supposed. The ratio of sitting to standing height varied from 47.2 to 52.8 per cent, but only I. J., who was very fat, approached closely the average normal

value of 52.9 per cent given by Hrdlička [18] for "old Americans" or that of 52.4 per cent given by Bean (cited by Hrdlička) for soldiers. The ratio of span to stature varied from 105.5 to 110 per cent, being in all instances well in excess of the averages for most races cited by Hrdlčka. The arms and legs were therefore disproportionately long. Delayed fusion of the epiphyses which commonly unite with their corresponding metaphyses after the age of puberty was characteristic, and was present in all but 1 of our patients.

Assays of the urine for androgenic and estrogenic material (table) were performed in the department of biochemistry, under the direction of Prof. F. C. Koch, and the methods and results have been discussed in detail elsewhere.[14] Benzene extracts of hydrolyzed urine were sep-

Excretion of Androgen and Estrogen in Cases of Hypogonadism in Men *

Patient	Age, Years	Condition	Period of Collection	International Androgens, Units per Day	Estrone (Theelin), Micrograms per Day	Ratio of Androgen to Estrone
A. B.	29	Eunuchoid	7 days	15	2	7.5
C. D.	26	Eunuchoid	7 days	28	2	14.0
E. F.	29	Eunuchoid	7 days	7	1	7.0
G. H.	24	Eunuchoid; cryptorchid	6 days	18	2	9.0
I. J.	20	Eunuchoid; cryptorchid	6 days	17	7	2.4
K. L.	36	Eunuchoid; cryptorchid	3 days	33	..	...
Average.....		6 eunuchoids	3 to 7 days	20	2.8	8.0
Average.....		Normal men	6 weeks	67 (40†)	10	6.7
Average.....		Normal women	6 weeks	47 (28†)	25	1.9

* Based on the data of Kenyon, Gallagher, Peterson, Dorfman and Koch.[14b]

† Values are based on boiling urine for two hours before extraction. In the rest of the determinations the urine was hydrolyzed fifteen minutes before extraction. The average normal values of 67 and 47 international units of androgens were calculated on the assumption that a 40 per cent loss occurs between the fifteen minute and the two hour hydrolysis.

arated by distribution between aqueous alkali and ether for the separation of the androgenic and the estrogenic fraction, the androgenic fraction remaining in the ether. The androgenic fraction was assayed according to the technic of Gallagher and Koch by injection into 7 capons and the influence on the comb compared with that of a standard preparation injected into comparable birds at the same time. The values are expressed in terms of the international standard, namely, the activity of 0.1 mg. of pure androsterone. The estrogenic fraction was assayed on 10 adult spayed rats according to the vaginal spread technic of D'Amour and Gustavson and compared with a known amount of pure estrone. The values are expressed in terms of 1 microgram of estrone (10 international units). Hydrolysis with acid before extraction is known to be necessary to secure the maximum yield of estrogenic material, and it has recently been observed that brief hydrolysis (fifteen

18. Hrdlička, A.: The Old Americans, Baltimore, Williams & Wilkins Company, 1925.

minutes) increases the yield of androgenic material by about 66 per cent over that obtained by the conventional two hour hydrolysis or none at all.[19] It is to be remembered that these assays do not measure single chemical substances but that one is dealing with mixtures of more or less unknown nature.

Previous studies on 4 normal young men for periods of six weeks showed a daily average for each of 40 international units of androgenic material, with a range of from 13 to 79 units, by the method of two hour hydrolysis. On the basis of hydrolysis for fifteen minutes, this would approximate an average of 67 international units, with a range of from 22 to 132 units. Many other individual assays were in agreement with these values. These normal men excreted the equivalent of from 2 to 29 micrograms of estrone in the urine, with an average of 10 micrograms.[14a]

In contrast, the 6 eunuchoid persons studied showed an average value of 20 international units of androgenic material per day with the fifteen minute hydrolysis (as compared with approximately 67 international units), with a range of from 7 to 33 units. Seven assays on 4 of these patients, studied by the two hour hydrolysis method, gave an average of 11 international units, with a range of from 0 to 17 units, as compared with the normal average of 40 units. Thus, no matter what duration of hydrolysis is chosen, the eunuchoid patients excreted about a third of the normal amount of androgenic material.[14b]

Five eunuchoid patients studied for estrogenic material excreted the equivalents of 2, 2, 1, 2 and 7 micrograms of estrone, respectively, as compared with the normal of 10 micrograms.

During treatment with large amounts of an extract of the urine of pregnant women for six months or more, there were observed in 2 patients slight enlargement of the penis and increase in erections, but little more. In 1 patient such treatment was accompanied by remarkable advances in sexual development at the age of 29, similar to the changes observed in normal boys at puberty; whether these changes were coincidental in this instance or were brought about by the treatment cannot be determined. These results are much like those secured in cryptorchid boys, except that striking changes are apparently more difficult to produce in the adult.[20]

Psychiatric study revealed nothing characteristic for the group. This is in accord with the opinion of Löwenthal,[11] based on a study of the

19. Peterson, D. H.; Gallagher, T. F., and Koch, F. C.: The Effect of Acid Hydrolysis on the Yield of Androgenic and Estrogenic Activities from Human Urine, J. Biol. Chem. **119**:185-188, 1937.

20. Thompson, W. O.; Bevan, A. D.; Heckel, N. J.; McCarthy, E. R., and Thompson, P. K.: Treatment of Undescended Testes with Anterior Pituitary-Like Substance, Endocrinology **21**:220-229, 1937.

literature, that the sexual defect is the only feature which eunuchoid patients have in common, that otherwise they differ from one another as other men do and that the claim of a specific eunuchoid psyche is untenable. Fraenkel [4] described 6 patients of his own and concluded that the view that there is a definite psychic structure in eunuchoid persons cannot be upheld. He commented that the psychic picture shows irregular polymorphism. On the other hand, Sterling,[2] Fischer [3] and Krisch [5] expressed the view that eunuchoid persons present a characteristic psychologic picture. Krisch divided them into three groups, viz., a group showing normal intelligence, but frequently exhibiting epileptoid and vasomotor symptoms; a feebleminded group, and a group showing outspoken epilepsy with a high degree of feeblemindedness. Sterling mentioned three types: viz., a type in which there is normal intelligence, but passive resignation to the sexual defect and to all difficulties; a type with imbecility, and a parasitic type, in which there is entire incapacity for the simplest work, with dependency, discontent and hypochondriacal complaints. Fischer described the eunuchoid person as having in common with the epileptic patient such traits as egocentricity, a demanding attitude, irritability, sensitiveness and pedantry, but contrasted the eunuchoid character as passive and the epileptic as active; he expressed the opinion that the essential difference is the lack in the eunuchoid person of the socially significant activity of the epileptic patient.

No feeblemindedness was present in the 6 patients whom we studied. One patient could be classified as of dull normal intelligence, on the basis of an intelligence quotient of 83 in the Stanford-Binet test. In the remaining patients the intelligence ranged from this point to the intellectual capacity required for successful college and professional work. This is in keeping with the view expressed by others that the feeblemindedness observed in some eunuchoid persons is to be referred to coincident developmental disturbances (Falta [6]) and that the presence or absence of intelligence has nothing to do with eunuchoidism (Peritz [9]).

No evidence of attacks of unconsciousness or convulsions was noted by us. We did not observe the so-called epileptic character in our patients. It is probable that in a larger group one would find persons exhibiting the clinical picture of the epilepsies. Frank psychotic manifestations were absent, although 1 patient showed a reaction of severe depression with suicidal thoughts at one period.

Peritz [9] reported a study of the psychic and social adjustment of 52 patients with eunuchoidism for whom the data were collected by means of a questionnaire sent to physicians. Of these patients, 22 had been seen in clinics or private practice, while 30 were inmates of hos-

pitals for mental disease or homes for the incurable. In the group there were 7 epileptic, 7 schizophrenic and 4 feebleminded subjects and 3 patients with other psychoses. Peritz stated that there is no definite relation between schizophrenia and hypogonadism. The group was divided into persons (31) who were adjusted socially and were successful in life and those (20) who were asocial or antisocial. As might be expected, there was a greater incidence of feeblemindedness, epilepsy, psychosis and poor social adjustment among those who were inmates of hospitals. Owing to the manner in which Peritz recorded the psychologic traits in his series of patients, it is difficult to evaluate his findings. One obtains the impression from his description that there is no characteristic picture except that the institutional patients tend to show more indications of poor emotional adjustment, such as dependency, indifference and timidity, than the noninstitutional group.

The subjects studied by us showed no specific personality pattern other than the emotional reaction to their physical defect as such, and even in this regard the degree of such reaction varied from subject to subject; thus, the reaction of C. D. was extreme, while that of K. L. was minimal. The lack of initiative, submissiveness, cowardice, ever. but indifferent disposition and pessimism, which were said by Sajous [21] to characterize eunuchoid persons, was not apparent. The description given by Climenko and Strauss [7] of conspicuous lack of pugnacity, softness of character, weakness and tendency to seek the protection of others does not apply to our patients. The comment by Gordon [22] that "there are psychic peculiarities due to attempts at adjustment with accepted social procedures" may be noted. The behavior of our patients was obviously influenced by attempts to adjust to accepted social procedure, as seen in the attitudes they formed toward marriage and sexual relations. Comment may be made on the attitude of society toward persons with eunuchoidism, as manifested in the life histories we have presented. The ridicule to which the patients were subjected as early as 10 years of age and the depreciatory attitude toward them when adults influenced their reactions to no small degree. The personalities of the patients varied from that of an active, energetic, popular, friendly, successful professional man (K. L.) to that of a quiet, withdrawn, sensitive, shy, self-conscious person (E. F.) or of an overfastidious, perfectionistic, pious, ambitious, quiet, reserved man (C. D.), who suffered keenly from his physical inferiority to the point of feelings of

21. Sajous, L. T., in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1928, vol. 3, p. 186.

22. Gordon, M. B.: Juvenile Endocrinopathies, in Piersol, G. M.; Bortz, E. L., and others: Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, 1934, vol. 5, pp. 176-205.

reference, depression and suicidal thoughts and who tried to solve his problems finally by seeking refuge in training for the priesthood. It is of interest to note that all 6 of our patients voluntarily sought treatment for their condition.

Fischer [3] described the eunuchoid personality in early and late childhood as well as in adult life. The description for the period of childhood he obtained from the anamnesis. He stated that eunuchoid persons as children are timid, dull and dependent, mingle poorly with other children, prefer to be alone, are anxious and are difficult to approach. In late childhood they were said to be mentally inert, sensitive, capricious, resistive and irritable and to show little mental agility in fantasy or in play. At puberty he portrayed them as exhibiting epileptoid symptoms, showing an increase in sensitiveness and in frequency of attacks of anger, becoming dissatisfied and indolent, showing a marked tendency to piety and complaining much of headaches. It is still later, he claimed, that outspoken signs of an epileptoid nature, as well as migraine and attacks of vertigo, appear. While some of our patients showed certain of these features during the developmental period, there was great individual variation. For the most part, outspoken behavioral reaction was absent until the age of puberty was reached.

The influence of heredity on the 6 patients described does not seem conclusive. In the case of C. D. both grandfathers and an uncle were psychotic, and 2 uncles were alcoholic. In the case of G. H. 1 cousin had had a mental illness. In the case of I. J. a sister had been mentally ill, and a brother had died of convulsions. In the case of the other 3 patients there was no evidence of mental or nervous disease in the family history.

The influence of the early environment and the family attitudes on our patients seems relatively unimportant so far as overt factors go, except in the case of C. D., on whose later adjustment the attitudes of both the father and the mother had an important effect. To a lesser degree, the overprotection which his mother gave E. F. as the youngest of the family influenced his later behavior.

With regard to the sexual life of our patients, the following summary may be given: Only 1 married. Three had had sexual intercourse with orgasm, but without ejaculation. Three had masturbated during early adolescence, with orgasm and no ejaculation. All had had erections. Three had nocturnal sexual dreams without emission. Four had sexual desire, while 1 reported no, and another very slight, desire. Five had been attracted to women during adolescence at least, but 2 later avoided contacts with women. Five had more men than women friends. No indication of perversion was noted in any patient, though 1 (C. D.) had been called homosexual by his fellow employees. Peritz [9] recorded

that 10 of the 52 patients studied by him were married, 8 had had sexual intercourse, 18 had sexual desire and 19 had erections. He mentioned 1 patient as being homosexual. Fischer [3] described a case in which homosexuality appeared after transplantation of a testis. Löwenthal [11] mentioned transvestitism in a case described by Falin.

In the group studied by us the primary and secondary sex characters were developed as in the normal boy of from 12 to 15; the physiologic aspects of the sexual life seemed similarly retarded, and the urinary excretion of androgenic and estrogenic substances amounted to one-third the excretion of normal persons. Except for the emotional reactions to the physical defect as such and the tendency to avoid an active sexual life, the group did not exhibit a specific personality pattern. Such evidence does not allow us to conclude that there is a close etiologic relationship between the existing hypogonadism and the psychologic picture presented. The group is too small, however, to permit general conclusions.

Superficial consideration might lead to the expectation that eunuchoids would show not only a tendency to a feminine body habitus but also feminine personality characteristics, and even homosexual trends. Such expectations were not borne out in this study. Although there was reduction in the urinary excretion of the estrogens as well as the androgens, this should not be held responsible for the absence of inversion, as homosexuality has not yet been shown to be in any way dependent on estrogenic secretion.

The question of the degree of influence of the endocrine glands on the psyche and of the psyche on the functions of the endocrine glands is still open. This is the old and familiar problem of psychosomatic interrelationships (Dunbar [23]). That there is a close etiologic relationship between the glands of internal secretion and mental disorders is not a conclusion that is compelled by the evidence in the literature, as Hoskins [24] has pointed out with reference to the psychoses and endocrine dysfunction.

It is suggested that psychoanalysis of eunuchoid patients may prove an important contribution to an understanding of the relationship of the endocrine glands and mental disorders. In this connection, it may be recalled that Freud, although he stressed the importance of trying to grasp psychologic facts psychologically, stated his belief that it will be demonstrated some day that the basis of the neuroses lies in the hormones.

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23. Dunbar, H. L.: Emotions and Bodily Changes, New York, Columbia University Press, 1935, p. 595.

24. Hoskins, R. G., in Bentley, I. M., and Cowdry, E. V.: The Problem of Mental Disorder, New York, McGraw-Hill Book Company, 1934, pp. 234-238.

SUMMARY

Six men with eunuchoidism were studied from the point of view of the physical, endocrine and psychiatic characteristics. No typical personality pattern was observed. The group showed an average urinary excretion of androgenic and estrogenic substances per day amounting to one-third that of normal persons. During treatment for long periods with an extract of the urine of pregnant women there were observed slight changes in 2 patients and remarkable advances in sexual development, similar to the changes in normal boys at puberty, in another. A discussion of these findings as compared with those previously reported in the literature is given. The group studied is too small to permit general conclusions. The need for further study along these lines is emphasized, and the use of the psychoanalytic technic is suggested as a valuable means of investigating the psychosomatic interrelationships in eunuchoidism.

DEPENDENCE OF SENSATION OF PAIN ON CUTANEOUS IMPULSES

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Many experiments have been made to test the sensitiveness to painful stimuli of internal organs and membranes.[1] These experiments were made with the cutaneous nerve endings functioning and did not rule out the possibility that pain is referred—that it may be due to afferent impulses coming from the skin to an irritable zone in the spinal centers. Mackenzie [1a] suggested that stimuli from an inflamed viscus set up an irritable focus in the cord and that the sensation of pain is referred to the peripheral distribution of the cerebrospinal nerves that traverse that focus. Head [1b] described in great detail zones of referred pain associated with visceral disease. Morley [1c] denied the existence of such a "viscerocutaneous reflex" and ascribed visceral pain to peritoneal irritation. Weiss and Davis [2] reported that they had obtained temporary relief from visceral pain by anesthetizing localized areas of skin to which the pain was referred. Their findings supported Mackenzie's theory of visceral pain by showing the importance of blocking cutaneous afferent impulses that reach the cord at the visceral level. Rudolf and Smith [3] confirmed this work; they found that proper cutaneous anesthesia was obtained by the injection into the epidermis of a 2 per cent aqueous solution of procaine hydrochloride, but not by subcutaneous infiltration of the solution. Pollock and Davis [4] analyzed the various pathways for the transmission of pain impulses from the peritoneal surface of the diaphragm.

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1. (*a*) Mackenzie, J.: Symptoms and Their Interpretation, ed. 4, London, Shaw & Son, Ltd., 1920. (*b*) Head, H.: On Disturbances of Sensation with Especial Reference to the Pain of Visceral Disease, Brain **16**:1, 1893. (*c*) Morley, J.: Abdominal Pain, Edinburgh, E. & S. Livingstone, 1931. (*d*) Ryle, J. A.: Visceral Pain and Referred Pain, Lancet **1**:895 (May 1) 1926. (*e*) Capps, J. A.: A Clinical Study of Pain, New York, The Macmillan Company, 1932. (*f*) Hurst, A. F.: The Sensibility of the Alimentary Tract, London, Oxford University Press, 1911.

2. Weiss S., and Davis, D.: Significance of Afferent Impulses from Skin in the Mechanism of Visceral Pain, Am. J. M. Sc. **176**:517 (Oct.) 1928.

3. Rudolf, R. D., and Smith, A. G.: Observations on Visceral Pain, Am. J. M. Sc. **180**:558 (Oct.) 1930.

4. Pollock, L. J., and Davis, L.: Visceral and Referred Pain, A. Research Nerv. & Ment. Dis., Proc. **15**:210, 1935.

Following the lead of Weiss and Davis, I made subcutaneous injections of an anesthetic in oil solution in cases of referred visceral pain and obtained relief from pain for several weeks. Oil-soluble anesthetics when injected subcutaneously produced prolonged anesthesia of the skin.[5] The solution was then employed in cases of pain of somatic origin, associated with localized areas of hyperalgesia or hyperesthesia of the skin. Anesthetization of such localized zones relieved somatic pain, just as it abolished referred visceral pain. Blocking afferent impulses from the skin was successful in abolishing localized pain, whether the focus of irritation was in a viscus, a ganglion (herpes), a nerve trunk (neuralgia), a bursa, a ligament or a muscle.

MATERIAL

The anesthetic solution was one which I had used in treatment of pruritus ani; the injection was painless and the solution produced anesthesia of the skin about the anus for about four weeks. It consisted of 3 per cent ethyl aminobenzoate, 5 per cent benzyl alcohol and 1 per cent phenol in expressed oil of almond U. S. P. The chemicals were dissolved in the sterilized oil. The addition of 5 per cent benzyl alcohol to the solution of ethyl aminobenzoate in oil intensified and prolonged the anesthetic action of the latter. Addition of 1 per cent phenol also increased the anesthetic action of the solution and insured its sterility. Profound anesthesia was produced for pain (pinprick) and for heat, cold and touch, but pressure sense was retained.

TECHNIC OF INJECTION

Only patients were selected for treatment who presented localized areas of pain, associated with zones of hyperalgesia or hyperesthesia of the skin as determined by pressure and pinprick. When pain was vague or diffuse or when the cutaneous zones of hypersensitivity were not distinct, the area of injection was too indefinite for treatment. The largest region that was treated had a diameter of 5 inches (12.7 cm.). After sterilization of the skin, the needle was inserted into the center of the area and was passed to the subcutaneous layer. Care was taken not to inject the solution into the epidermis, as the oil is slowly absorbed and may cause pressure necrosis if introduced into the firm layers. The syringe was then attached, and the needle was passed to the margin of the zone of hypersensitivity. The contents were aspirated to make certain that no blood vessel had been entered. The anesthetic oil was then injected slowly while the needle was being withdrawn to the point of puncture. Usually four injections were made, crosswise to each other and for equal distances. When the diameter of the zone was large, between 4 and 5 inches (10 and 12.5 cm.), from six to eight injections were made, the lines radiating from the center like the spokes of a wheel. The injections were made slowly and evenly, about 0.5 cc. being allowed to each square inch (6.45 sq. cm.) of surface and care being taken not to pool the oil about the site of the cutaneous puncture. The needle was then withdrawn, and the skin was gently massaged to distribute the oil more evenly throughout the hyper-

5. Yeomans, F. C.; Gorsh, R. V., and Mathesheimer, J. H.: Benacol in the Treatment of Pruritus Ani, M. J. & Rec. **127**:19 (Jan. 4) 1928. Gabriel, W. B.: Treatment of Pruritus Ani, Brit. M. J. **1**:1070 (June 15) 1929.

sensitive zone. If an excess of the solution was injected or it was introduced too superficially into the skin, the area became slightly distended and tender to pressure for a few days. The presence of soreness on pressure, associated with freedom from the original pain and complete anesthesia to pinprick and touch, was probably due to irritation of the pressure nerves resulting from the reaction of the subcutaneous tissue to the solution. The volume of solution injected in a single zone varied from 0.5 to 10 cc., depending on the area. The maximal total amount employed for a patient was 10 cc. During the injection there was no discomfort. About one hour later some patients had a slight burning sensation, not described as pain, that lasted for three hours. In some patients slight ecchymosis of the area of injection occurred, but gradually disappeared. The chemicals employed did not produce any toxic symptoms, and no infection occurred. The ages of the patients ranged from 19 to 72 years.

CONDITIONS TREATED

1. *Herpes Zoster* (6 cases).—The distribution was intercostal, with scattered zones of papules and vesicles and hyperalgesia of the surrounding skin. From 0.5 to 2 cc. of the anesthetic solution was injected into the subcutaneous tissue below each area. The largest number of cutaneous zones in these cases was five. There was prompt relief from pain, which did not recur when the anesthesia wore off, four weeks later.

2. *Femoral Neuralgia: Meralgia Paraesthetica* (3 cases).—There was an area of hyperesthesia, 5 inches (12.7 cm.) in diameter, over the upper and outer aspects of the thigh. Ten cubic centimeters of the oil was employed to complete the injections which were made in eight directions from the point of puncture of the skin. The paresthesia was supplanted by a feeling of numbness which disappeared gradually in from three to four weeks, but the paresthesia did not return.

3. *Bursal Pain: Subacromial-Subdeltoid Bursitis* (6 cases).—Abduction of the arm caused severe pain in the shoulder, radiating to the neck and down the arm. Zones of tenderness were present about the acromioclavicular joint and the insertion of the deltoid muscle on the humerus. These occurred singly or together. A circle of hyperesthesia, 2 inches (5 cm.) in diameter, was present about the acromioclavicular joint. When the bursa of the deltoid muscle was also involved, another area of hypersensitivity, 3 inches (7.6 cm.) in diameter, was present just above the level of insertion of the deltoid muscle. Treatment of the acromioclavicular zone required 2 cc. of the solution, injected subcutaneously in four crosswise directions from the point of puncture of the skin. Injection into the deltoid area was made in six directions from the center of the hypersensitive zone. Immediately after completion of the injections the patient was able to abduct the arm without pain.

4. *Articular Pain: Sacroiliac Sprain* (7 cases).—Tenderness was present over the posterior iliac spine, and bending the trunk caused severe pain in that region. A zone of hyperesthesia, from 2 to 3 inches (5 to 7.6 cm.) in diameter, was present about the area of tenderness. From 2 to 5 cc. of the oil was injected subcutaneously, depending on the size of the hypersensitive area. The injections were made radially in from four to six directions from the point of maximal tenderness. Immediately after the injection the patient could bend the body without pain. A residual sensation of "weight" or "pressure" remained, which was referred to the sacroiliac joint.

5. *Muscular Pain: Lumbago* (2 cases).—In these cases the pain was secondary to an attack of grip. Bending the trunk caused pain in the lower lumbar muscles.

A rectangular zone of tenderness and hyperesthesia, 2 inches (5 cm.) in width and 5 inches (12.7 cm.) in length, was located on either side of the spine, and extended downward from the third or fourth lumbar vertebra to the sacrum. A needle 2½ inches (6.4 cm.) long was inserted 1 inch (2.54 cm.) lateral to the spine, and 5 cc. of the solution was injected subcutaneously, parallel to the spine, above and below the point of insertion. This longitudinal area of injection extended the length of the region of hypersensitivity. A similar injection was made on the opposite side of the spine. The skin was massaged in a lateral direction to distribute the oil throughout the subcutaneous area. After the treatment muscle spasm relaxed, and pain on movement of the trunk was relieved. There remained sensation of "heavy pressure," which was localized within the muscles.

6. *Visceral Pain.*—Carcinoma of the Stomach (1 case): The tumor was inoperable. Severe, sharp pain was referred to the midepigastrium. Nausea and vomiting were frequent. A localized zone of hyperesthesia was present in the midepigastrium, 3 inches (7.6 cm.) in diameter. Subcutaneous injection into this area of 5 cc. of the oil relieved the pain for three weeks, but the nausea and vomiting persisted. (Nausea and vomiting are direct reflexes involving the higher centers.)

Carcinoma of the Gallbladder (1 case): Severe pains were present in the right upper quadrant of the abdomen. A cutaneous zone of hypersensitivity, 3 inches (7.6 cm.) in diameter, was present in the same region. Subcutaneous injection of 5 cc. of the oil into this area in four directions relieved the pain up to the time of operation, two weeks later. A sensation of deep pressure, with occasional nausea and vomiting, persisted after the pain was gone.

COMMENT

The results recorded indicate that the sensation of pain is dependent on the presence of cutaneous impulses. The relief from pain in cases of somatic as well as of visceral disease obtained by blocking the afferent impulses from the skin to the cord can best be explained by extending Mackenzie's theory of referred visceral pain to include the skeletal tissues: An irritable focus in the central nervous system develops when it is bombarded with stimuli from an inflamed visceral or skeletal structure, which lowers the threshold for afferent impulses from the ectoderm entering the system at the level of that focus. Other theories to explain the abolition of referred pain by anesthesia of the skin, such as "cutaneous shock" or absorption of the anesthetic along the nerve trunks, have been discussed by Rudolf and Smith and have been found unconvincing.

The fact that pain disappears immediately after anesthetization of the skin in cases of bursal, muscular and articular diseases indicates that the afferent nerves from these tissues to the cord do not carry direct pain impulses. After relief from pain, the residual sensation of "weight" or "pressure" localized in the part affected represents the sensation of the irritated sensory receptors within these tissues. That the defensive and protective mechanism of the primitive pain sense should

be confined to the surface of the body is in keeping with the phylogenetic and embryonic development of the nervous system, which is an inward growth of the ectoderm.

The relief from pain in cases of herpes and neuralgia obtained by blocking cutaneous impulses suggests that the sensation of pain is due to specific impulses arising from cutaneous pain nerves. In these cases the original pain was due to lesions in a dorsal root ganglion of the spinal cord (herpes) or a nerve trunk (neuralgia), but after the cutaneous impulses were blocked the central sensorium no longer recorded pain.

The objection may be made that not only were the terminal nerves to the skin anesthetized by subcutaneous injection but trunks of sensory nerves carrying pain fibers from the deeper structures may have been blocked by the anesthetic. If, however, a sensory nerve trunk was anesthetized, areas of anesthesia would be expected beyond the local zone of treatment; this did not occur. Furthermore, the sensory branches to the skeletal structures enter these tissues at a distance from the subcutaneous layer into which injection was made. It is also improbable that gentle massage of the area of injection forced the solution to the skeletal structures concerned, as relief from pain occurred in most instances directly after completion of the injection, before the skin was massaged.

CONCLUSIONS

1. A solution of an anesthetic in oil is described which when injected subcutaneously produces prolonged anesthesia of the skin.

2. Anesthetization of localized areas of hyperalgesia and hyperesthesia in the skin relieves pain arising from deeper structures, whether visceral or skeletal.

3. The relief from pain in cases of herpes and neuralgia obtained by blocking the cutaneous impulses indicates that the sensation of pain is dependent on specific pain impulses from the skin to the central sensorium.

4. Pain from skeletal or visceral tissues is referred to the skin and may be explained by a modification of Mackenzie's theory of visceral pain: An irritable focus in the central nervous system develops when it is bombarded with stimuli from an inflamed visceral or skeletal structure, which lowers the threshold for afferent impulses from the ectoderm entering the system at the level of that focus.

PATHOGENESIS OF SYRINGOMYELIA

CASE ILLUSTRATING THE PROCESS OF CAVITY FORMATION FROM EMBRYONIC CELL RESTS

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Although cavity formation in the spinal cord was described first by Estienne (or Stephanus), a pupil of Sylvius, in 1545, and later by Morgagni, the term "syringomyelia" was suggested by Olivier d'Angers in his "Treatise on the Spinal Cord and Its Diseases," in 1837. He applied the term not to a specific pathologic entity but to any cavity or canal in the cord. He expressed the belief that the presence of a central canal was abnormal. It was not until 1859, when Stilling began the investigation of the development of the canal, that d'Angers' conception was disproved.

Among the earlier modern theories was that suggested by Hallopeau,[1] who expressed the opinion that certain types of myelitis resulted in cavity formation; he concluded that the primary lesion was sclerosis in the region of the central canal. Virchow and Leyden [2] later maintained that all medullary cavities were really offshoots of the central canal.

Simon [3] was the first to describe cavity formation resulting from the softening of gliomas and their subsequent absorption. He expressed the belief that the term "syringomyelia" should therefore be applied only to cavitation independent of the central canal. This was the incentive for the great mass of pathologic and clinical investigation conducted during the latter part of the nineteenth century. Charcot, quoted by Bruhl,[4] gave credit to Schultze and Kahler for first clinically delineating the disease.

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From the Division of Neuropsychiatry of the Stanford University School of Medicine.

1. Hallopeau, H.: Contribution à l'étude de la sclérose diffuse périépendymaire, Gaz. méd., Paris **25**:394, 1870.

2. Leyden, E.: Klinik der Rückenmarkskrankheiten, Berlin, A. Hirschwald, 1875, vol. 2, pt. 1.

3. Simon, T.: Beiträge zur Pathologie und pathologischen Anatomie des Centralnervensystems, Arch. f. Psychiat. **5**:108, 1875.

4. Bruhl, I.: A Contribution to the Study of Syringomyelia, translated in Selected Essays and Monographs, London, The New Sydenham Society, 1897.

Schultze [5] concluded that the process was due to abnormal development of ependymal cells with subsequent breakdown of proliferated glial cells and first called the condition "gliosis."

At this period three noteworthy monographs appeared, which may still profitably form the basis for further study. Bäumler [6] collected and analyzed 112 cases reported in the literature and demonstrated that the condition is not one of the *rara et curiosa,* as Erb had previously stated, but not infrequently is first discovered at autopsy and is often associated with congenital anomalies. Bruhl [4] described the sensory *dissociation syringomyélique,* the Aran-Duchenne type of muscular atrophy with main en griffe and varied trophic disturbances as diagnostic only of the variety of syringomyelia which is due to gliomatosis of the cord, a "lesion of the neuroglia." He failed, however, to find a cause for the excavation of the gliotic tissue. Most significant of the three monographs was that of Schlesinger,[7] who observed that in the great majority of cases the *Centralkanalepithel* lines part of the cavity. He concluded that "the central gliosis formed from the epithelium of the central canal" and that the cavity resulted from melting down of the newly formed tissue. Changes in the blood vessels were said to be of importance in cavity formation, but to be secondary to the central gliosis. Other types of cavity formation were recognized, notably those due to trauma, inflammatory softening, degeneration of tumor tissue and primary vascular changes.

We present the study of a case of syringomyelia, followed by a discussion of some of the more recent pathologic conceptions, in an effort to demonstrate that syringomyelia, *sui generis,* is a definite pathologic entity and to speculate on the progression of the process. Our case is of particular interest because the disease involved a great length of the cord, and various stages of the pathologic process can be traced.

REPORT OF CASE

L. N., an American railroad worker aged 47, entered the clinic on Aug. 7, 1920, complaining of severe pain in the back and left leg and inability to extend the left leg. In 1907 he had fallen, injuring the legs. After this he became increasingly lame and had much pain in the back and left hip, which continued and progressed slowly until his admission to the clinic. About a month previous to his admission the left leg became fixed in flexion; efforts to extend it were painful. The past and family histories contained nothing of significance.

5. Schultze, F.: Klinisches und Anatomisches über die Syringomyelie, Ztschr. f. klin. Med. **13**:523, 1888.

6. Bäumler, A.: Ueber Höhlenbildungen im Rückenmark, Deutsches Arch. f. klin. Med. **40**:443, 1887.

7. Schlesinger, H.: Die Syringomyelie, ed. 2, Leipzig, Franz Deuticke, 1902.

Examination.—The patient was well developed and moderately emaciated. There was marked scoliosis of the spine to the right. The left leg was contracted, and the muscles of the left thigh were atrophied. The left knee joint was much larger than the right. The left foot was moderately edematous, and the toes were cyanotic and scaly. Blisters were present on the heels.

There were left hemiatrophy and fibrillation of the tongue. The hamstring muscles of the left leg were spastic. The abdominal and cremasteric reflexes were absent; the knee and ankle jerks were hyperactive on the left, and the Babinski sign was present on this side. Sensations of pain and temperature were impaired below the level of the fourth thoracic segment bilaterally, while touch remained intact in the same area. Vibration sense was impaired in both lower extremities; there was no ataxia. There were no noteworthy symptoms or signs referable to the upper extremities.

The Wassermann reaction of the blood was negative, and the spinal fluid was normal.

Course.—On December 16, because of severe and intractable pain, chordotomy was performed on the left side at the level of the sixth thoracic vertebra (eighth thoracic segment of the cord), with some relief. The patient entered the clinic in 1926 complaining of pain, which had reappeared a few months previously. Sensations of pain and temperature were diminished over the entire body, especially the thighs and arms. The left side was more affected than the right. Touch was still unimpaired. Vibration sense was absent in both lower extremities. Nystagmus was present.

On Dec. 17, 1926, a second chordotomy was performed at the level of the third thoracic vertebra, with relief from pain. Three days after the operation bronchopneumonia developed, and the patient died four days later.

Necropsy.—The lungs were edematous and congested. There were areas of early consolidation, and the bronchi contained blood-stained froth. There was generalized arteriosclerosis. The other essential changes were in the central nervous system, which was removed and fixed in a dilute solution of formaldehyde U. S. P. (1:10).

Macroscopic Examination: The meninges of the spinal cord were thickened throughout, especially in the cervical and thoracic regions. The cord was extremely irregular throughout most of its length, with marked anterolateral flattening between the fourth and the sixth thoracic segment. Between the seventh and the ninth thoracic segment there was a region of cystic degeneration, 3 cm. long and 1 cm. wide. There were cavities throughout the cord, except in the midthoracic and lower lumbar and sacral portions (fig. 1). The cavities extended cephalad through the medulla. The cerebral hemispheres were normal.

Microscopic Examination: Pyroxylin sections were made from every segment of the cord and from the cortex, midbrain and medulla. The following stains were used: hematoxylin and eosin, cresyl violet, phosphotungstic acid hematoxylin, Mallory's aniline blue and orange G and the Van Gieson, Alzheimer-Mann and Pal-Weigert methods.

In the medulla a slitlike cavity on the left side separated the inferior olivary nucleus from the corticospinal tract. This was continuous with the cavitation in the upper cervical segments, where bilateral slits ran dorsolaterally toward the entrance of the dorsal roots, extending to the meninges. These slits were continuous with each other just posterior to the central canal and in most places were lined ventrally by ependymal cells. The greater portion of the posterior horns was lacking; the anterior horns, too, had become involved. The lepto-

meninges were markedly thickened by fibroblastic proliferation, especially near the dorsal roots, where many psammoma bodies had formed.

Lower in the cervical region the cavity was larger, running laterally through the region of the central canal. The ependymal lining was present and in the sixth cervical segment lay both ventrally and dorsally, in no place, however, completely lining the cavity. The anterior and lateral horns were better preserved, although the posterior horns were still obliterated. The leptomeninges were not as thick here as at a higher level. In the central part of the cavity at the sixth

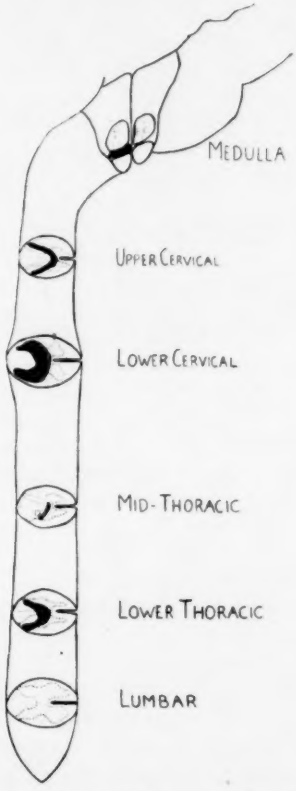

Fig. 1.—Diagrammatic sketch of ependymal cell rests and cavitation. The ependymal cells are indicated by white areas; the cavities are black. Cavitation in the left side of the medulla separates the inferior olivary nucleus from the pyramidal tract. There are no cavities in the midthoracic region, but lines of ependymal cells are present. The lower lumbar and sacral regions are normal.

cervical segment was a well developed psammoma body with an epithelial lining, which was identical with the ependyma of the cavity.

In the upper thoracic portion of the cord the region of the central canal was strikingly abnormal; there were many irregular linear groups of ependymal cells, some partially lining cavities. Spongioblasts and their derivatives in places streamed away from the bases of the ependymal limiting membrane. The large Y-shaped cavity, continuous with the cavity in the cervical region and occupying the central part of the cord, was lined for only a short distance by the primitive

cells. It contained a débris of myelin sheaths, glia cells and thickened blood vessels. Some of the ependymal lining had sloughed into the cavity; other cell groups were not in linear form but possessed nuclei similar to those of the cells just described. Just above the ventral median septum of the fourth thoracic segment were several collections of cells of ependymal origin, some in linear order and some in clusters. Dorsally, almost in the midline, a long row of ependymal cells lay adjacent to a thick-walled vessel.

From the fifth to the seventh thoracic segment the cord was markedly compressed and the anatomic arrangement destroyed. In cross section it measured 11 by 2 mm. Here was no cavity formation. Extending from the ventromedian part of the cord dorsolaterally in either direction, corresponding to the position of the cavity in other segments, was an area of gliosis in which myelin sheaths were almost lacking. There was no central canal, but on either side were collections of cells resembling filled-in central canals. Near one of these groups was a row of ependymal cells, 0.8 mm. in length. There was considerable formation of vacuoles, especially in the gliotic area. Amylaceous bodies were numerous, as in other parts of the cord. A few hyalinized, swollen ganglion cells remained. The gliotic process extended into the remainder of the cord.

In the seventh thoracic segment the distortion of the cord was so marked that normal structures could not be identified. The gliotic areas were increased and irregularly distributed. The eighth thoracic segment consisted for the most part of a large cystic cavity which had penetrated the meninges and was filled with spinal cord tissue and hyperplastic glia cells. "Cell rests," including lines of ependymal cells, were present in both segments. Many blood elements were scattered through the tissue. The leptomeninges were markedly hyperplastic.

Below the eighth thoracic segment a Y-shaped cavity trisected the cord, leaving a central wedge-shaped area in which only moderate gliosis had taken place and the myelin sheaths were relatively intact. Another long row of ependymal cells lined the cavity ventrally, extending ventrally to what was probably the central canal. The anterior horns were again recognizable, although most of the cells were degenerated. In the upper lumbar region the cavities became smaller and slitlike, with vessels running adjacent to the walls, as was seen in the upper cervical portion of the cord. In the lower lumbar region and caudally the cord was normal, except for thickening of the walls of the blood vessels.

Ependymal lining: The columnar cells of the ependymal lining were widest at the internal limiting membrane, beneath which they tapered gradually; many had filamentous tails, which stained with phosphotungstic acid hematoxylin (fig. 2). The internal limiting membrane was thick and refractile. Occasionally blepharoplasts were present just beneath the limiting membrane. None of the cells possessed cilia. The nuclei were situated near the tails; they were oval and contained an evenly distributed chromatin network and several coarse chromatin granules. There were also many mature ependymal cells without tails.

Near the ependymal lining were nests of cells with similar nuclei. The cytoplasm stained poorly. Their arrangement was for the most part irregular, although there was some pseudorosette formation around the numerous capillaries.

Where there were no linear groups of ependymal cells, some of the cavities, especially in the cervical and thoracic regions, were lined with spongioblasts of various types: unipolar, bipolar and, less often, multipolar (fig. 3). In general, the farther lateral from the center of the process were the neuroglia cells the more mature was the type.

The glial tissue surrounding the cavities was usually distinctly demarcated from the fiber tracts and the gray matter. There was little evidence of any

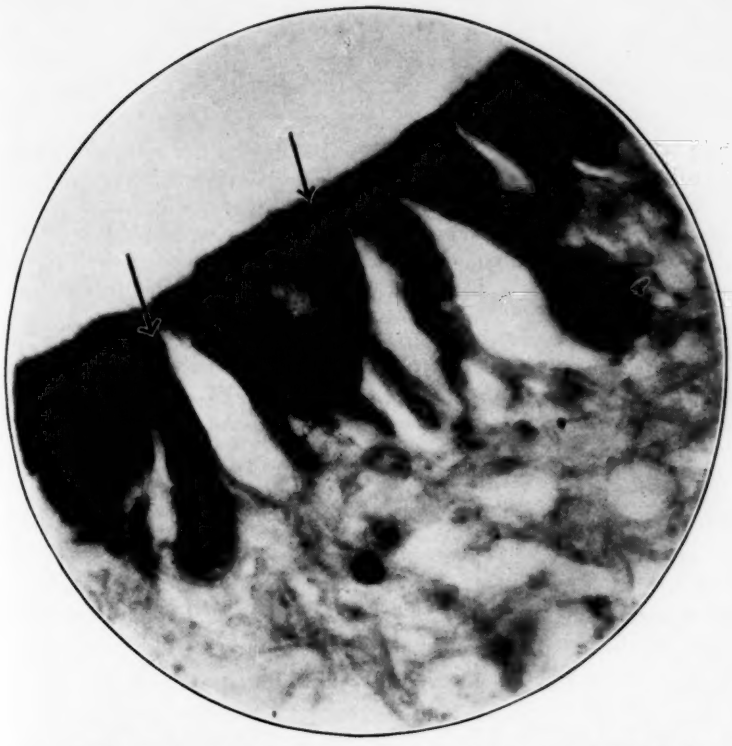

Fig. 2.—Ependymal spongioblasts lining the cavity at the level of the eighth cervical segment. Blepharoplasts are indicated by arrows. The internal limiting membrane is not shown. Phosphotungstic acid hematoxylin stain.

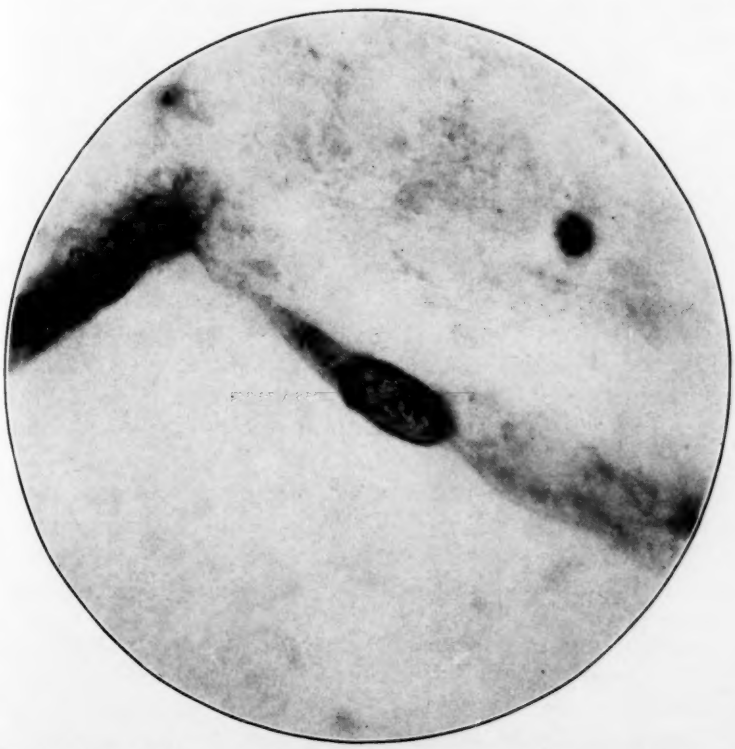

Fig. 3.—A unipolar spongioblast lining the cavity at the level of the seventh cervical segment. Phosphotungstic acid hematoxylin stain.

active destructive process, as shown by the absence of gitter cells, gemästete cells and perivascular infiltration. Where cavitation had occurred in the gray columns there were many apparently normal ganglion cells at the brink of the cavity. In some places near the cavitation glia cells were in pseudopalisade formation.

Vascular changes: Throughout the cord, vessels with greatly thickened adventitia swarmed in from the hyperplastic pia. Some resembled simple strands of collagen, but with higher magnification an endothelial lining and blood cells were seen. Some of these vessels lay at the border of the cavities and others inside. Some occurred in "vascular islands" (figs. 4 and 5). Hassin[8] recently discussed these islands and cited the *encapsulations* of Petrén, the *formations conjonctivo-vasculaires* of Thomas and Hauser and the "vascular aggregations" of Cerletti.

COMMENT

The ependymal bands and other cell nests in this case are of particular interest. The process causing these formations, which we consider to be veritable "cell rests," must a priori be the basis of syringomyelia. The case reported is an exquisite example of such rests. Throughout the cord, except in the lower lumbar and sacral regions, were linear groups of ependymal cells, including many primitive ependymal spongioblasts. These groups formed a partial lining for much of the cavitation. Some writers have expressed the belief that these cells grow outward from the central cavity to line the syringomyelic cavity and are only the manifestations of a secondary process. However, extending from the fifth to the eighth thoracic segment, where there were no cavities, not only these long rows of cells but scattered, circumscribed collections of similar cells forming nests (figs. 6 and 7) were observed. Here, also, there was no definite central canal, either open or obliterated. This is evidence that these cells do not play a secondary role, but precede and determine rather than follow cavitation.

When the lines of ependymal cells are traced from a portion of the cord where there was no cavity formation to the midcervical region, for instance, where cavitation was marked, the formation of an ependymal lining of the cavities may be explained. Cavitation might start not at the ependymal limiting membrane but in the surrounding gliotic tissue, which underwent necrosis and subsequent absorption (fig. 7). This absorption was noted in all stages: Some of the cavities were filled with débris; others were empty and well defined. In some parts of the cord the cavitation encroached on a row of these cells, the row continuing laterally, where it was completely surrounded by gliotic tissue (fig. 8). This tissue, which also became necrotic, might slough and be absorbed and the ependymal cells line the cavity (fig. 9). The strong ependymal limiting membrane seemed to form an effective barrier against the further advance of cavity formation. The cavities were never com-

8. Hassin, G. B.: A Contribution to the Histopathology and Histogenesis of Syringomyelia, Arch. Neurol. & Psychiat. **3**:130 (Feb.) 1920.

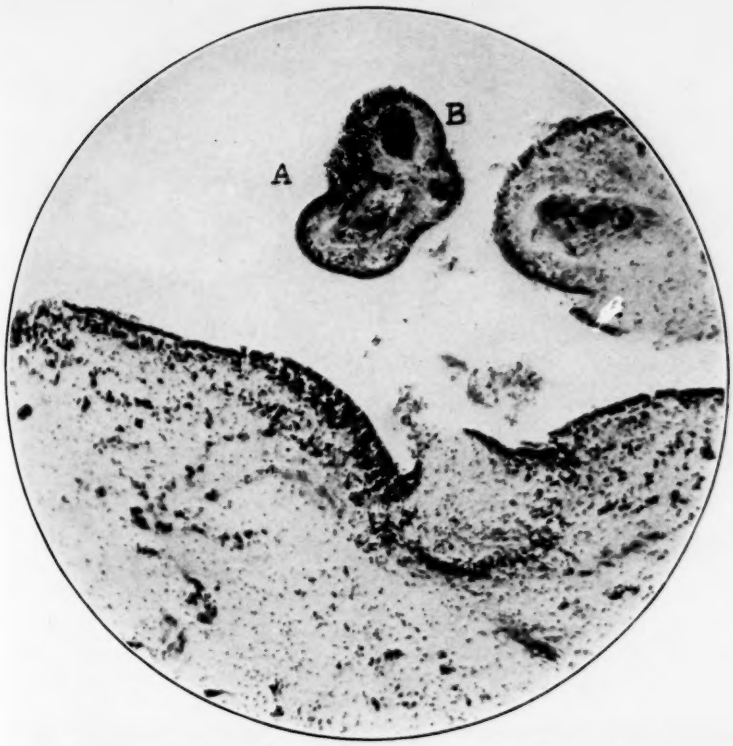

Fig. 4.—"Vascular island" (*A*) bordered by ependymal cells and containing blood vessels (*B*), at the level of the sixth cervical segment. Hematoxylin and eosin stain.

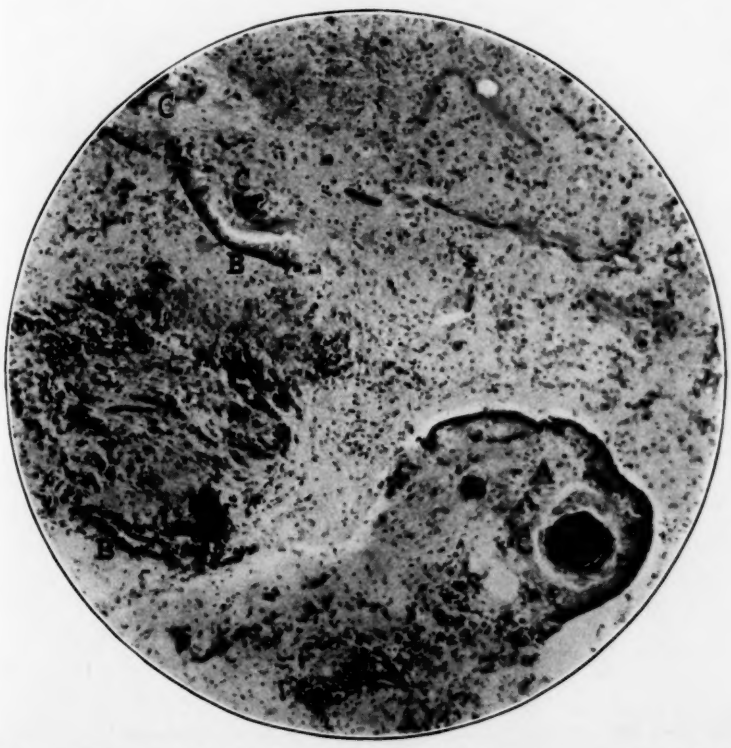

Fig. 5.—"Vascular island" (*A*) in a stage of formation at the level of the fourth thoracic segment. This should be compared with the stage shown in figure 4. Lines of ependymal cells (*B*) are present. Blood vessels (*C*) lie adjacent to some of these lines. Hematoxylin and eosin stain.

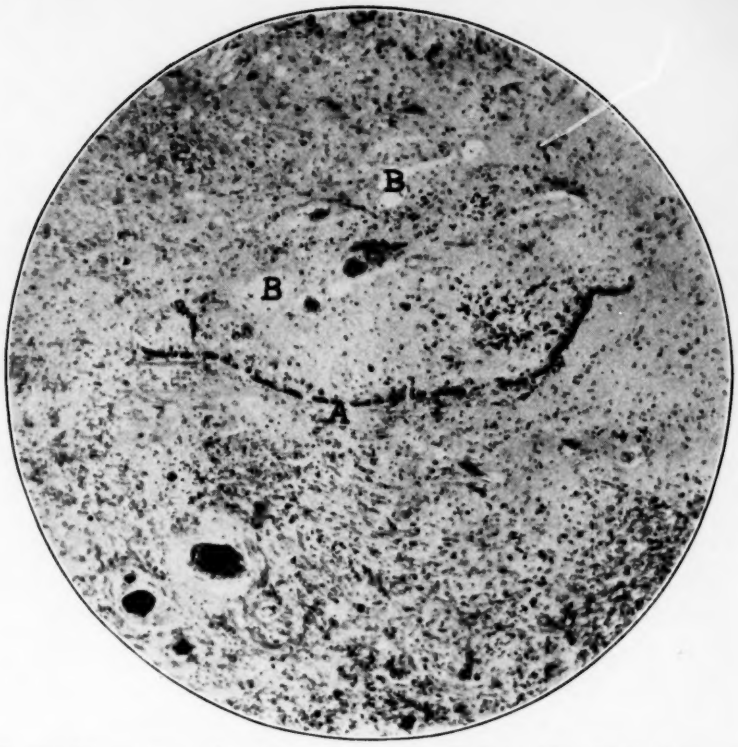

Fig. 6.—Line of ependymal cells (*A*) surrounded with gliotic tissue at the level of the fifth thoracic segment. Beginning vacuolation (*B*) is present. Hematoxylin and eosin stain.

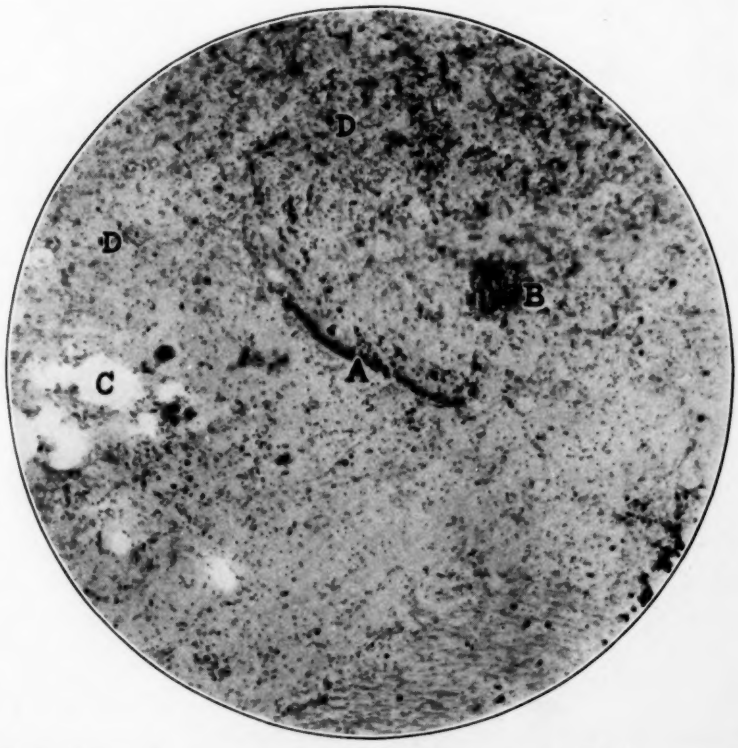

Fig. 7.—Line of ependymal cells (*A*) and a circumscribed nest composed of similar cells (*B*) at the level of the seventh thoracic segment. The breakdown of gliotic tissue (*C*) is more advanced than that shown in figure 4. Amylaceous bodies are shown at *D*. Hematoxylin and eosin stain.

Fig. 8.—Second thoracic segment. The breakdown of glial tissue has partially encroached on the ependymal cells (*A*). Necrotic tissue is breaking down at the ependymal membrane (*B*). Hematoxylin and eosin stain.

Fig. 9.—Sixth cervical segment. The cavity is lined with ependyma. Some débris remains. Psammoma bodies (*A* and *B*) are present in the cavity. Hematoxylin and eosin stain.

pletely surrounded with ependyma. There was no evidence to show that any of the cavitation was due to simple enlargement of the central canal, as in hydromyelia, or that the ependymal cells grew outward from the central canal to line the cavity.

The term "syringomyelia" in such a case is misleading in that cavitation is only an end result of the process. Hoffmann [9] called it "primary central gliosis." Mackay and Favill,[10] who reported a case in which there was a coexisting ependymoblastoma, further suggested the term "primary ependymal gliosis," stating that the glial proliferation takes place from the primitive ependymal spongioblasts, which differentiate into mature ependymal cells and astrocytes.

That such "cell rests" are present in the spinal cord without associated syringomyelia is a matter of record. Schlesinger [7] reported cases in which there were abnormal inclusions of glia cells in the posterior commissure of the cord. Zapport, cited by Riley,[11] observed great variation in the central canal, with extensions in all directions. Rolly [12] described multiple canals and other abnormalities in the spinal cord of 3 children. He questioned whether typical syringomyelia might have developed if the patients had lived. Ependymal hyperplasia is extremely frequent in the center of the cord, according to Cornil and Mosinger,[13] sometimes comprising a veritable benign asymptomatic tumor. These authors failed, however, to observe the hyperplastic process in any of their cases of syringomyelia or hydromelia. Incidentally, they studied the central canal in a series of 66 cases in which the cord was normal: In 19 cases the canal was open; in 16 there was partial obliteration, and in 31—almost half—there was total obliteration. Scott, LeFever and Oliver [14] described a case in which there were scattered rests of ependymal cells in the central gray matter.

Gliosis is necessarily of slow development. Whether it starts at birth or later is impossible to say, but there must be considerable gliosis before symptoms are manifest. The onset is gradual and the course usually

9. Hoffmann, J.: Zur Lehre von der Syringomyelie, Deutsche Ztschr. f. Nervenh. **3**:1, 1892-1893.

10. Mackay, R. P., and Favill, J.: Syringomyelia and Intramedullary Tumor of the Spinal Cord, Arch. Neurol. & Psychiat. **33**:1255 (June) 1935.

11. Riley, H.: Syringomyelia or Myelodysplasia, J. Nerv. & Ment. Dis. **72**:1, 1930.

12. Rolly: Ueber periependymäre Wucherung, Kanalbildung und abnorme Entwicklungsvorgänge am kindlichen Rückenmarkkanal, Deutsche Ztschr. f. Nervenh. **21**:355, 1902.

13. Cornil, L., and Mosinger, M.: Sur les processus prolifératifs, de l'épendyme médullaire (rapports avec les tumeurs intramédullaires et la syringomyélie), Rev. neurol. **1**:749, 1933.

14. Scott, E.; LeFever, H., and Oliver, M.: Syringomyelia and Syringobulbia, Ohio State M. J. **30**:223, 1934.

prolonged. Both embryonic and mature glia cells, including spongioblasts and macroglia cells, are present in the gliotic area. This indicates that the gliosis is a result of further differentiation of primitive spongioblasts, similar to the normal embryonic development of glia cells from the germinal layer of the neural tube. There is no evidence of an active destructive process. The gliosis is ordinarily well demarcated from the surrounding tissue of the spinal cord, and normal ganglion cells and myelin sheaths sometimes lie immediately adjacent to it; gitter cells are lacking.

Investigators have held that syringomyelia results from the breakdown of tumor tissue, a theory recently suppored by Pette and Környey.[15] The process, however, differs from that in ordinary medullary gliomas in that (1) its course is longer; (2) it follows the vertical axis of the cord; (3) the cellular arrangement does not suggest any definite histologic type of tumor, and (4) it does not tend to invade surrounding tissue. Syringomyelia may therefore be considered a benign and regressive phenomenon. To debate whether syrinx formation is attributable to the breakdown of tumor tissue is merely to argue over the definition of "tumor." In our opinion, cavitation in a circumscribed tumor is not true syringomyelia.

Many other authors have concluded that syringomyelia results from a developmental anomaly. Other forms of cavitation may be called pseudosyringomyelia, as suggested by Philippe and Oberthür.[16] Bielschowsky and Unger[17] proposed that failure in the differentiation of spongioblasts, with resultant spongioblastoma, is the pathogenic factor. Henneberg and Koch[18] expressed the belief that the process responsible is atypical closure of the canal, leaving cell masses of incomplete development. Marinesco and Draganesco[19] stated that the fundamental process is failure of migration of spongioblasts.

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15. Pette, H., and Környey, S.: Zur Kenntnis der Rückenmarksgliome mit Ausgang in Syringomyelie, zugleich ein Beitrag zur diffusen meningealen Ausbreitung des Glioms, Deutsche Ztschr. f. Nervenh. **117-119**:371, 1931.

16. Philippe, C., and Oberthür, J.: Classification des cavités pathologiques intra-médullaires: I. Syringomyélie vraie; forme cavitaire et forme pachyméningitique; II. Pseudo-syringomyélies (hydromyélie; hématomyélie; cavités vasculaires; cavités traumatiques), Rev. neurol. **8**:171, 1900.

17. Bielschowsky, M., and Unger, E.: Syringomyelie mit Teratom- und extramedullärer Blastombildung: Zur Kenntnis der Pathogenese der Syringomyelie, Jahrb. f. Psychiat. u. Neurol. **25**:173, 1920.

18. Henneberg, R., and Koch, M.: Zur Pathogenese der Syringomyelie und über Hämatomyelie bei Syringomyelie, Monatschr. f. Psychiat. u. Neurol. **54**: 117, 1923.

19. Marinesco, G., and Draganesco, S.: Kyste épidermoïde cholestéastomateux de la moelle épinière coexistant avec un processus syringomyélique, Rev. neurol. **31**:338, 1924.

Association of syringomyelia with congenital anomalies in one third of Schlesinger's cases [7] is substantiating evidence that syringomyelia is a developmental malformation. Haenel [20] reported cases in which there coexisted cervical ribs, spina bifida, meningocele, hydrocephalus and microgyria. Bremer [21] postulated a familial constitutional defect; he observed that asymmetry of the mammary glands, pigeon breast and scoliosis occur not infrequently as a family characteristic. He grouped these malformations together as "status dysraphicus." Recently, Weil and Matthews [22] described the case of a child aged 5 months with duplication of the spinal cord associated with spina bifida and syringomyelia.

The cause of the association of syringomyelia and primary intramedullary tumor is not clear, although it is well established. Kernohan, Woltman and Adson [23] reported 5 of 9 cases of such tumors in which syringomyelia was present and 5 of 12 cases of syringomyelia in which there was a coexisting tumor. This frequent coexistence of a primary intramedullary tumor, especially ependymoma, and syringomyelia may perhaps be explained by the presence of circumscribed cell nests, as already described. These nests may proliferate and form the tumor.

Hyperplasia of the meninges or primary vascular changes have been suggested as the basic condition in syrinx formation (Davison and Keschner [24]). In our case, however, the hypertrophy of the meninges and of the vascular adventitia and the formation of psammoma bodies were necessarily secondary to the gliosis. Hassin [8] stated that increased pressure due to fluid in the cavities is another factor in cavitation.

Actual cavity formation may be accounted for by anoxemia resulting from the vascular changes. While thrombi are lacking, there are slowing of the blood stream in the tortuous, thick-walled vessels and resultant congestion. Cobb [25] said:

> Congestion is a common cause of anoxemia, and if severe enough it causes increased permeability of the capillary walls with diapedesis and eventually necrosis.

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20. Haenel, H.: Syringomyelie, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1911, vol. 2, p. 572.

21. Bremer, F. W.: Klinische Untersuchungen zur Aetiologie der Syringomyelie, der "Status dysraphicus," Deutsche Ztschr. f. Nervenh. **95**:1, 1926.

22. Weil, A., and Matthews, W. B.: Duplication of the Spinal Cord with Spina Bifida and Syringomyelia, Arch. Path. **20**:882 (Dec.) 1935.

23. Kernohan, J. W.; Woltman, H. W., and Adson, A. W.: Intramedullary Tumors of the Spinal Cord: Review of Fifty-One Cases with Attempt at Histologic Classification, Arch. Neurol. & Psychiat. **25**:679 (April) 1931.

24. Davison, C., and Keschner, M.: Myelitic and Myelopathic Lesions: VI. Cases with Marked Circulatory Interference and a Picture of Syringomyelia, Arch. Neurol. & Psychiat. **30**:1074 (Nov.) 1933.

25. Cobb, S.: A Preface to Nervous Disease, Baltimore, William Wood & Company, 1936.

Blood cells were observed outside the vessels in our case, and some of the cavities were almost completely lined with blood.

It is frequently mentioned in the literature, as in our case, that the patient dated the disease from an injury. Some authors have attributed the whole process to trauma. Tauber and Langworthy [26] recently published the results of an experimental study in which they concluded that occlusion of the anterior spinal artery causes central cavitation because this portion of the cord receives only terminal arterial branches. They suggested that concussion causes a diminished blood supply through the effect of arterial spasm on this relatively avascular part of the cord. Edema and subsequent compression result in necrosis; gliosis follows. In our case trauma was not the primary factor; that it played an important role in the process would be merely an assumption. The trauma was not remarkably severe, and the paralysis did not appear immediately but developed slowly and progressively. The wide distribution of cell rests cannot be explained by trauma.

SUMMARY

A case of syringomyelia is presented. In it we believe that we have traced the process of cavity formation from ependymal cell rests.

1. Linear arrangements of ependymal cells were present throughout the cord, partially lining the cavities in some segments and existing purely as rests in segments in which no cavitation had occurred.

2. Cavitation began in the surrounding gliotic tissue and extended to the ependymal limiting membrane, so that the linear rests eventually lined the cavity.

CONCLUSION

This study suggests that syringomyelia, *sui generis,* is a developmental anomaly caused by imperfect formation of the central canal by primitive medullary epithelium. Resultant cell rests later undergo gliosis. Cavitation in the poorly nourished gliotic tissue is an end result of the process. Syringomyelia is therefore a heterotopic and benign process, which may be differentiated histologically from tumor formation by the lack of characteristic proliferative and invasive gliosis.

Dr. W. F. Schaller provided us with the pathologic material and clinical data.

26. Tauber, E. S., and Langworthy, O. R.: A Study of Syringomyelia and Formation of Cavities in the Spinal Cord, J. Nerv. & Ment. Dis. **81**:245, 1935.

THE INVOLUTIONAL MELANCHOLIA PROCESS

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The more closely the processes in mental disease are examined the more they are found to betray certain characteristic stigmas at all stages of their development.[1] In its manifestation of homogeneity of process involutional melancholia has a peculiar distinction. So characteristic is this homogeneous pattern that we feel justified in designating it "the involutional melancholia process." This study, begun in September 1935, at the suggestion of Dr. Edward A. Strecker, had as its aim the critical examination of the total life pattern of a number of persons suffering from involutional melancholia, the collection of data regarding prepsychotic personality traits, the course and prognosis of the disease and the formulation, if possible, of a total concept of the disorder.

We shall endeavor to bring more clearly into the light some striking facts about the prepsychotic personality of patients suffering from the disease and to relate these facts to the onset and course of the psychosis itself. We shall also try to evaluate other factors, such as the relation of the course and prognosis to predominant traits, predictability of the psychotic episode and the weight and quality of the precipitating situation. We hope also to bring involutional melancholia to proper recognition as a clinical entity, disengaged from consideration with manic-depressive psychosis.

REVIEW OF LITERATURE

The historical perspective of melancholia has received distinguished treatment by Jelliffe,[2] in a consideration of the manic-depressive synthesis, and, more recently, by Blalock,[3] in a clinical investigation of the

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Read by title at the Ninety-Third Annual Meeting of the American Psychiatric Association, Pittsburgh, May 14, 1937.

From the Institute and the Department for Mental and Nervous Diseases of the Pennsylvania Hospital and the Department of Psychiatry, the University of Pennsylvania School of Medicine.

1. Cheney, C. O.: Trends in Psychiatric Research, Psychiatric Quart. **10**:224 (April) 1936.

2. Jelliffe, S. E.: Some Historical Phases of the Manic-Depressive Synthesis, A. Research Nerv. & Ment. Dis., Proc. **11**:3, 1931.

3. Blalock, J. R.: Psychology of the Manic Phase of the Manic-Depressive Psychosis, Psychiatric Quart. **10**:262 (April) 1936.

manic-depressive psychosis. Certain recognized textbooks of psychiatry [4] contain excellent presentations of the development of this concept. The literature regarding involutional melancholia in periodicals, however, is surprisingly small, and a review covering the past twenty years (from 1916 to 1936) is ample to convey the significant developments contained therein.

The modern classic concept of the involutional melancholia syndrome was first formulated by Kraepelin.[5] This had its birth simultaneously with the broad differentiation of the two major psychotic groups, the manic-depressive and the schizophrenic. For many years thereafter (up to 1907), the disease was generally held to be a clinical entity with a variable prognosis. The transitions which the concept of the disease underwent about that time have been traced by Hoch and MacCurdy [6] and Henderson and Gillespie.[7] In 1907 there appeared an article by Dreyfus[7a] which, for reasons that are difficult to understand, changed the whole clinical concept of involutional melancholia and accounts for the relegation of the disease to the category of the manic-depressive psychosis. Curiously, Kraepelin concurred entirely and, in the later edition of his textbook, spoke of involutional psychoses as essentially manic-depressive in nature. However, subsequent study (Kirby) showed that in the cases reported by Dreyfus the data were analyzed carelessly and erroneously. Opinion, among psychiatrists in general, as to the nature of the illness has shown a wide diversity during the past fifteen years, as reflected by various contributions to the subject in medical periodicals. Young [8] accepted the classic description of the disease as he observed it in southern communities and gave a detailed discussion of the prodromal period. Menninger [9] made a distinction between the mild, transient psychogenic depressions, so often met in general practice, and the serious syndrome which he called simply "melancholia." Somewhat later, Grozin [10] presented arguments against classifying involu-

4. (*a*) Noyes, A. P.: Modern Clinical Psychiatry, Philadelphia, W. B. Saunders Company, 1934. (*b*) Strecker, E. A., and Ebaugh, F. G.: Clinical Psychiatry, ed. 4, Philadelphia, P. Blakiston's Son & Co., 1935.

5. Kraepelin, in Bleuler, E.: Textbook of Psychiatry, translated by A. A. Brill, New York, The Macmillan Company, 1924.

6. Hoch, A., and MacCurdy, J. T.: Prognosis of Involution Melancholia, Arch. Neurol. & Psychiat. **7**:1 (Jan.) 1922.

7. Henderson, D. K., and Gillespie, R. B.: Textbook of Psychiatry, ed. 3, New York, Oxford University Press, 1933.

7a. Dreyfus, in Henderson and Gillespie.[7]

8. Young, F. F.: Involution Melancholia, New Orleans M. & S. J. **83**:375 (Dec.) 1930.

9. Menninger, K.: Melancholy and Melancholia, J. Kansas M. Soc. **21**:44 (Feb.) 1921.

10. Grozin, M.: Involution Melancholia, M. Rev. of Rev. **37**:397 (July) 1931.

tional melancholia with the manic-depressive psychosis. He did not take up directly the etiologic issue, but obviously implied a large psychologic factor. The concept of the relationship of the psyche and the soma in the illness was scouted by Menzies,[11] in an unconvincing article. The literature on the endocrinologic aspect of the disorder is singularly slight. Strecker and Keyes [12] published results of treatment with intramuscular injections of an extract of corpus luteum and ovarian substance. They concluded that the extracts exert a beneficial influence in a limited number of cases but that the endocrine factor is not solely responsible for the illness. Werner [13] and his co-workers obtained beneficial results from the judicious administration of estrogenic substances. They expressed the belief that they had solved the problem of the cause of the disease and that it may now be established as an endocrine disorder.

We believe, however, that one is still a long way from solving the etiologic problem in this disorder, that the cause may reside in a subtle combination of psychic and somatic factors as yet unfathomed and that the problem in general may be considered open to investigation.

In a study of the menopause in relation to psychosis, Farrar and Franks [14] asserted that there is not a materially greater frequency of mental disabilities in women during the fifth decade than at other times of life. Involutional melancholia seemed to occur in women of a special type of character makeup, and not to represent a general tendency in the particular life period.

Henderson [15] called involutional psychoses "anxiety states at the involution period." He showed that the depressed phase of the manic-depressive syndrome is much more the sad, slow, retarded variety of depression, with the special accent of a subjective feeling of difficulty in thinking. Vestiges of the manic phase of the manic-depressive psychosis, which Dreyfus observed in his patients with involutional melancholia, are wholly absent. If expansive ideas are present in the disease at all they are of the bizarre mixed depressive and grandiose character, as in the patient of Weygandt's who expressed the belief that she was going to be boiled in a silver kettle. The absurd, fantastic

11. Menzies, W. F.: Mechanism of Involution Melancholia, J. Ment. Sc. **66**: 355 (Oct.) 1920.

12. Strecker, E. A., and Keyes, B. L.: Ovarian Therapy in Involution Melancholia, New York M. J. **116**:30 (July 5) 1923.

13. Werner, A. A., and others: Involution Melancholia: Probable Etiology and Treatment, J. A. M. A. **103**:13 (July 7) 1934.

14. Farrar, C. B., and Franks, R. M.: Menopause and Psychosis, Am. J. Psychiat. **10**:1031 (May) 1931.

15. Henderson, D. K.: Anxiety States Occurring at the Involutional Period, J. Ment. Sc. **66**:274 (July) 1920.

forms of the delusions are characteristic of the illness. Concerning the "megalomania" of the involutional syndrome, such as it is, Jelliffe and White [16] said:

> The megalomania may be manifested by such beliefs as that the patient is the greatest sinner in all the world or the worst criminal that ever existed. The self-love and egotism are symptomatic also of a degree of narcissism that makes these patients almost inaccessible to therapeutic approach.

The masochistic, self-inculpatory character of the megalomania is thus evident. The insistent flow of ideation in the patient with involutional melancholia, to which we referred previously, is always of a strictly stereotyped nature; the patient repeats over and over the same delusions of sin, death and poverty. Never does he show anything remotely approaching the clang associations, circumstantiality or labile ideation of the manic patient. Henderson said:

> The mechanism of the involution melancholic case seems to be much the same as that of the anxiety neurosis except that in the psychosis the conduct of the individual is less under control. The psychosis acts as a safety valve, allowing expression of doubts and fears (e. g., as regards incestuous conflicts, etc.) repressed in normal life.

CLINICAL MATERIAL

METHOD OF STUDY

In 1935 Bond [17] offered a method for abstracting the data in cases which combines the virtues of condensation and photographic elucidation of dominant trends in the personal history. The advantages to be derived from the method are extraordinary, considering the brevity and ease with which the abstracts may be prepared. The entire course of the patient's life, from birth to and through the psychosis, is sifted so as to allow placement on a single page, in isolated, terse sentences or paragraphs relevant to each phase of life. Of these abstracts, Bond said: "To let the abstract spill over to a second page, as we were tempted to do, produced a result which was awkward. These abstracts magnify family history, prepsychotic personality, life events, onset of psychosis and follow-up for five years after admission to the hospital and minimize the symptoms shown in the hospital unless they throw light on the earlier life history. . . . I think that the profile of a case on one sheet of paper is a remarkable instrument. It gives a view comparable to that of the low power microscope, in which some relationships are seen which escape the oil immersion."

Abstracts of this type seemed admirably suited to bring out in bold relief the characteristic features of involutional melancholia; accordingly, such abstracts were made for the 100 patients whom we studied, comprising 50 (25 men and 25 women) with involutional melancholia and 50 (25 men and 25 women) with manic-depressive psychosis. In further discussion, even more concise, cryptic

16. Jelliffe, S. E., and White, W. A.: Diseases of the Nervous System, ed. 5, Philadelphia, Lea & Febiger, 1929.

17. Bond, E. D.: Illustrations and Comparisons in the Affective and Schizophrenic Psychoses, New York, Morchand Press, 1935.

views of the personalities and trends representing condensations of these one page abstracts may be used to bring out points relating to the various phases of this study. Some personalities bear description in a few words; others require more copious elaboration.

PREDOMINANT PERSONALITY TRAITS

Analysis of the material shows that the involutional personality, from its earliest formative phase, reveals a quality of rigidity, inelasticity or unadaptability which predisposes it to make poor or faulty adjustment to the transitions of the involutional period, with its demands on the adaptive resources. Most striking is the even horizontal line which this personality trend maintains throughout, there being few or no evidences of cyclothymic upheaval, prominent swings of mood or definite psychotic eruption of the type peculiar to the manic-depressive disorder.

Personality Structure.—The type of personality which we found in patients with involutional melancholia, like any personality, has many facets; one may see it from various points of view, according to the individual makeup. With the general character of all patients essentially the same, individual patients showed special trends which indicated the most illuminating angle from which to study them; e. g., in some persons sadistic traits colored the whole personality picture which, as a *Gestalt* or total pattern, might be termed psychasthenic (compulsive). In other patients masochistic traits predominated. (Sadism and masochism are generally held to be reciprocal poles of a single fundamental instinctual distortion, but their quantitative diffusion in an individual personality generally has a definite unified direction.) Other patients showed clearly the evidence of lifelong constriction of the mental horizon. Still others showed from the earliest years the presence of unwholesome instinctual trends, such as parental fixations or dominations, heterosexual maladaptations or meagerness of interest and outspoken homosexuality. In some persons moral rigidity or hyperreligiousness constituted a fanatic devotion and absorbed a large quantity of the available energy. In several patients a number of these dominant trends were so fused that it was difficult to say which was uppermost. It is curious to note the uniformity with which a constricted horizon, sadism or masochism, a repressive note as regards pleasures and a perfectionist trend are blended in the personalities of patients with involutional melancholia.

CASE 8.—*Combination of unwholesome trends in fairly well saturated solution.*

A beamer in a mill, who worked steadily, never earned more than $45 a week. He married at the age of 34. His home life was never happy, owing to his peculiarities and abusive temper. He was always of a melancholy disposition. He drank heavily up to five years before the onset of the present illness. Whisky made him boisterous and excited. He occasionally went on short sprees. He

stayed by himself a great deal and objected to others in the family going out. He was unreasonable, abusive and quick tempered in talk, but not violent; he did not belong to any societies and did not care to mingle with others. He had few friends. He played a horn in his younger days, but not since marriage. He liked music, but never sought it. He worried easily whenever anything did not go just right. He was always argumentative, self willed and obstinate and hard to manage. He spent little for pleasure except that which was needed. He was said to like baseball, but he never went to the games.

CASE 29.—*A typical "schizoid" personality at work in development of the psychosis."*

A highly intellectual woman was graduated from a distinguished college at the age of 20. She was called an expert in mental analysis and liked research work. She later received a master's degree from a western university and taught in a private school for several years. She worked in the personnel department of a large department store. She was temperamental. She always took life too seriously. She longed to marry and have children but never made herself attractive to men. She was of the student type. Most of her friends were unmarried women. She was always precise and overfussy in her work.

CASE 32.—*An extroverted personality, with almost hysterical overdevotion to one set of interests, which made one suspect that the so-called extroversion was not as genuine as it appeared.*

At the age of 22, the patient married a physician with tastes similar to her own. Their married life was considered comfortable, unusually happy and full of interest. She was capable, but not overenthusiastic, as a housekeeper; she enjoyed the planning more than the details. Her worst problem was to provide a suitable lunch for her husband in the middle of the day. She kept two servants and had plenty of time for outside interests, such as church and club work. She was a member of various guilds and clubs of a literary or cultural nature. She was not interested in politics beyond knowing who the mayor was. The editorials and the first sheet of the newspaper interested her, and occasionally she read a book. Local attachments were strong; it meant much to her to be near the church, the provision dealers, the car line and the bus. She was a devout church woman and never missed a mass; the special church festivals meant much. She and her husband were abroad three times; they often went to the theater and opera together.

When extroversion was present at all, it was invariably complicated by a marked psychopathologic factor. The following patients were so-called extroverts.

Women: Patient 37 was considered an extrovert, but was "always a worrier over trifles" and had an obsessive personality.

Patient 30 was sociable and friendly, but had a markedly infantile personality. She made no sexual adjustment and broke down when an arrangement to live with a sister failed to materialize.

Patient 38, an extrovert, was irritable and anxious at menstruation and totally frigid in marriage. She neglected her family to help her mother, who later died of cancer.

Patient 42 had a "lively disposition," but was fastidious and overconscientious; she was a painfully slow, thorough housekeeper. The personality changed to one of marked introversion in the thirties.

Patient 41 was sociable and energetic, but was "more interested in her business than anything else."

Patient 50 worried easily and "crossed bridges" long before it was necessary.

Men: Patient 10 was a great "joiner"; he gave most of his energy to church and was overreligious.

Patient 13 was an ardent sportsman; he had been dominated by his first wife; when the second wife tried to rule him sadistic traits appeared; he was physically violent and forced his wife into perversions; he never had swings of mood.

Patient 20 had a "jolly disposition," devoted all his attention to his home and was excessively kind and gentle.

Patient 23 was a "jolly, steady worker" and a hard drinker; he showed an overdevout religious attitude.

Of both the men and the women patients, 20 of 25 (80 per cent) were markedly introvertive; in the other 20 per cent in each series there were pathologic factors, or the diagnosis was questionable.

The classic formation of reactions of obsessional (psychasthenic) character, in which stubbornness, parsimony and overmeticulosity or excessive cleanliness predominate, was so prominent in both the men and the women as to leave an overwhelming impression. Eighteen of the men showed reactions of an outspoken obsessional character.

Two patients who were treated by psychiatrists for years had a long-standing history of an overt obsessional neurosis. Brief intaglios of the obsessive personalities follow: "Meticulous, moved home to suburbs because of nervousness"; "regular as a clock about work"; "never missed a day's work, always excessively quiet"; "excessively clean and neat in habits, overconscientious"; "stubborn, argumentative and self willed"; "overmeticulous in everything, everything just so"; "close, penurious, eccentric"; "extreme regularity of habits, could set the clock by him"; "finicky about food, fussy in dress"; "worrier, meticulous about business"; "particular, overconscientious."

Among the women a history of such outspoken obsessive personality was not as frequent, 13 having a history of a marked trend of this sort. When the history of a definite compulsive tendency was lacking, the personality in each case was marked by another outstanding pathologic trend, such as refusal to gain any pleasure in life.

The preceding discussion has approached the patients chiefly from the standpoint of the note of "rigidity" in the life history. Others of the personalities may be approached through the common denominator of "repressive" characteristics, i. e., the presence of a strong puritanical trend, with hyperreligiousness, avoidance of all pleasure and deliberate refusal to take advantage of pleasurable experience of any kind. As the compulsive or "rigid" pattern was found to be present in practically undiluted proportion in 18 of the men and 13 of the women, it is in most cases merely a matter of which common denominator to take

account in evaluating the personality. The presence of the two trends so strongly fused in such a large number of the personalities points toward a parallelism or "symbiosis."

CASE 12.—*A strong repressive trend, combined with an obsessive character, seemed to be constitutional from early years.*

A clerk, who had been with one company since his late teens, was of an overly sensitive, quiet, melancholy nature. He preferred the company of men and boys, though he did not dislike women. He never married, and would not mention the subject of sex. He was of small stature and was self conscious about this. He did not show any ambition or ability in his work; he remained at the same working level for years. He was extremely regular in his habits; one "could set clocks by him." He lived according to a quiet routine. He arose, went to work, returned home, smoked a cigar and went to bed. On Sunday mornings he read the newspaper. He was always regular in church attendance. He never had any outside interests or hobbies. He never spent vacations away from home. He was generous with others, but rather miserly with himself. Usually he carried considerable funds with him in the form of bills, not trusting banks or investments.

CASE 11.—*Eccentric loneliness outweighing an extrovertive tendency, of paranoric character.*

A real estate man, of considerable shrewdness, never married and lived so much by himself that no one knew of his intimate affairs. He lived in a narrow circle, with no wide interests; yet he belonged to five lodges and had many friends among the farmers of the district in which he worked. Although a regular church member, he was never active in church affairs and was considered by many of his friends as eccentric. He lived in the same room in which he had his office. He was "close" and penurious. He went out, bought a little food and brought it back to his office, having no regular place to eat.

CASE 33.—*A personality analogous to that in case 11, from the group of women patients.*

A woman aged 48, brought up in a small mining town, dropped high school for a trivial reason and came to the city, where she worked alternately as a waitress and saleswoman and in other odd capacities, generally leaving because she was bored with the work. She was quiet, self conscious and sensitive. She did not care to go out to meet people. She gave up all work to take care of her invalid mother. She never had any relations with men. She later lived with her sister, but did not get along well even with her. Occasionally she went to the movies, but she demurred at other enjoyments.

Difficulties Involving the Instincts.—The presence of deep instinctual difficulties was noted in a high proportion of both the men and the women patients.

Sexual Adjustment and Marital Status: Some of the men avoided heterosexual life entirely or made a poor adjustment; others had unhappy marriages; still others evidently struggled to sublimate homosexual trends but did not succeed, as judged by the lack of a tone of satisfaction to the life as a whole.

Patient 1 "did not get on well with other men and was a poor mixer."

Patient 2 was separated from his wife shortly after marriage and had nothing to do with women again.

Patient 6 made a poor adjustment throughout his married life.

Patient 8 had an "unhappy home life, was a heavy drinker and had few friends."

Patient 24 was overattached to his mother, in spite of marriage and a family.

Patient 12 never married, had no heterosexual contacts and preferred the company of men and boys.

Patient 13 was dominated by the first wife; when coaxed into a second marriage, he became vengeful and stubborn and hoarded his funds.

Patient 14 had two unhappy marriages, both of which were broken up.

Patient 17 said: "Every one said I was a bachelor from a boy up." He had no heterosexual contacts.

Patient 22 avoided the company of other men, with anxiety.

Of the men, 22 were married. Of these, 12 were poorly adjusted to marriage; the remaining 10 were moderately well adjusted. Of the 12 who were poorly adjusted, only 2 recovered from the illness. However, of those who did not recover, 2 died of intercurrent causes (general debility and infection), and 1 committed suicide. The outcome was not much better for those who were comparatively well adjusted to marriage. Of these 10, 3 recovered entirely.

Only 15 of the women were married. Of these, 7 were poorly adjusted to marriage. In all the 7 patients the outcome of the psychosis was bad. Of the rest, 7 were well adjusted to marriage, and all recovered. Of the 10 unmarried women, 8 did not recover. Of the remaining 2, 1 recovered late, after an extremely prolonged course; the other recovered entirely. In other words, there was a relation between marriage and recovery. When there were marriage and poor adjustment the outcome was bad; when there were marriage and good adjustment the outcome was good; when there was no marriage (with bad sexual adjustment in each case) the outcome was bad.

These figures for both sexes, while chiefly impressive for the women, indicate the probable presence of a relationship between good sexual adjustment, through successful marriage, adequate sublimation or other channels, and the malignancy of the involutional psychosis and its eventful outcome.

Number of Children: Three of the men had 4 children each and were considered happily adjusted to the family life. Another man had 5 children, who succeeded and of whom he was proud. Another man had 4 children, but showed no special concern about them. Two of the men had children, but the exact number was not stated in the anamnesis; the attitude toward them was not known. Three of the men had 1 child each, but evinced no special attitude toward them. One man married a widow who had already had children; the venture was not a success. The other 12 married men were childless and showed indifference or antagonism to having children.

The women showed a better record in the matter of the number of children and their responses to them. One woman had 6 children and was happily adjusted to them. Four women had 3 children each; 1 of these felt that her children were ultimately a disappointment and that this was a factor in the onset of

the psychosis. Three women had children the number of whom was not stated. The reaction to having them was undetermined. Two women had 2 children each, and 3 women, 1 child each; none of these women showed any special attitude toward the children.

Attitude of the Women Toward the Menses: The findings corroborated those of Farrar, who noted that it appeared to be not the menopause or menstrual difficulty which constituted the pathologic factor but the individual outlook on these states. The findings did not point to any uniformity in the course of a stormy menopause or of chronic dysmenorrhea as a concomitant factor in involutional melancholia. In other words, it was impossible to say that the menopause and its attendant complications were an almost universally present factor in bringing on the disease. Nine women had a history of irregular periods or menopausal anxiety. The other 16 women were singularly free from such complications, the factor leading to downfall being something more relevant to the general psychologic state in the transitional era or definite trauma bearing a special import because of advancing age. Two patients attributed their psychosis directly to worry over the menopause. They did this spontaneously on admission to the hospital, without being questioned on this point. In these 2 patients only was there any discernible direct connection between the menopause and the illness. The other 7 women in whose psychosis menstrual factors played a role had chronic dysmenorrhea, with irritability and anxiety at each menstrual period. One woman felt guilty because of having intercourse during menstruation. Another was always excitable and unreasonable, and another irritable and fault finding, at the menstrual period. This was typical of the patients in whom menstrual factors played a role.

Developmental Adjustments: Although the anamneses generally did not bring out clearly the data regarding the specific point, evidence in early life of strong fixations of a libidinal character to parents or other close associates was not lacking. One man showed a strong masochistic father dependence. Another, who was educated by his sister, showed later sublimated evidence of this attachment. Another patient was oversubordinate to his brother throughout life. The mother was the mainstay of another, and there was evidence that she had pathologically conditioned both her sons. Still another man was overdependent on his father. One man indicted himself as a "stay-at-home," an ideal bachelor, and never went out with women. He lived with his mother, "a wonderful woman." Another man admitted that he was too attached to his mother; his marriage nearly broke up when he tried, with his wife, to live indefinitely with his mother. Later, he showed a full-blown compulsion neurosis.

Of the women, 1 was overprotected, pampered, much attached to her father and unsympathetic toward her mother. Another woman was sheltered, spoiled, passive and overattached to both parents. One woman was much attached to the mother, as evidenced by the fact that the psychosis was precipitated by the mother's death. One woman was masochistically attached to a sister, and 2 women showed strong homosexual fixations on sisters, wanting to live with them always. One woman neglected her family to live with her mother, who eventually died of cancer. Another woman was selfishly dependent on her daughter for twenty-five years. Another woman worried herself into a psychosis over the future of her mother and herself. In another, an incestuous fixation on the son was strongly hinted at; another woman was so strongly attached to her son as to be unable to break away.

We have summed up diagrammatically the personality trends which were found in these patients with involutional melancholia.

Men

Hyperreligiousness	12 (48%)
Sadomasochism	12 (48%)
Sexual maladjustment	15 (60%)
Strong voluntary or conscious repressive trend	17 (68%)
Obsessional (compulsive or psychasthenic) character	18 (72%)
Marked introversion	20 (80%)

Women

Hyperreligiousness	8 (32%)
Sexual maladjustment	8 (32%)
Stormy menstrual history	9 (36%)
Sadomasochism	13 (52%)
Obsessional character	13 (52%)
Strong conscious repression	20 (80%)
Marked introversion	20 (80%)

To sum up: Introverted personality, strong conscious repression, obsessional character and sexual maladjustment were the predominant trends and character difficulties in both the men and the women. Sadomasochistic tendencies were startlingly prominent in both sexes. Hyperreligiousness was a factor in both sexes. Disordered menstrual life of a chronic nature, with improper attitude toward the menopause, was a factor in only slightly over a third of the women—a notable finding.

PSYCHOPATHOLOGIC TRENDS IN THE INVOLUTIONAL PERSONALITY

Muncie,[18] in a study of the "rigid personality" in relation to psychosis in general, gave a concept of this biologic pattern. He said:

> Rigidity of personality is compounded in no fixed proportions, of many factors, such as obstinacy, aggressiveness, pride, sensitiveness, a rigid code of personal ethics, an inability to make concessions, a "hundred per cent attitude," etc. . . . These same qualities are like a two-edged sword, and many of the difficulties that beset the [psychotic] patient are directly attributable to them.

Muncie showed graphically how a rigid personality hinders recovery from psychosis. The main characteristics of the prepsychotic personality, as summarized by Titley,[19] are, in part:

> Narrow range of interests, poor facility of adjustment, asocial trends, inability to maintain friendships, intolerance and uniformly poor adult sexual adjustment. Likewise, the pronounced and rigid ethical code, the proclivity for saving, the profound reticence, the marked sensitivity, the outward evidences of anxiety, the notable stubbornness, the overconscientiousness and meticulosity in regard to person and work are present to some degree.

In Titley's [19] study of the prepsychotic personality in involutional states, the emergence of this personality as a distinct type was striking.

18. Muncie, W.: The Rigid Personality as a Factor in Psychoses, Arch. Neurol. & Psychiat. **26**:359 (Aug.) 1931.

19. Titley, W.: Prepsychotic Personality of Patients with Involutional Melancholia, Arch. Neurol. & Psychiat. **36**:19 (July) 1936.

There was not the remotest resemblance to the prepsychotic personality of the near normal or of the manic-depressive patients whom he studied. Courtney [20] pointed out rather dogmatically the absence of any relationship and even suggested that involutional melancholia is nothing more than psychasthenia with the barriers of inhibition swept away.

We believe that it is probable that the psychic changes in the involutional state play the largest role in the onset of the disorder. MacCurdy [21] said:

> There are specific arguments for its being essentially a psychological reaction. There are usually a definite mental precipitating cause and the appearance of specific ideas with which the other symptoms appear to be related.

It is remarkable that among women there is a definite tendency for the psychosis not to appear until five years after the menopause. Graves [22] said:

> In addition to unfounded fear of physical degeneration at this time, there is widespread apprehension of serious mental upheaval. Superior women pass through the menopause with little or no trouble.

Graves listed as further predetermining elements in the onset of the psychosis such factors as a stormy menstrual life, prolonged dysmenorrhea, anemia, constipation (indicating analogy to the anal-erotic constitution), nervous shock, great disappointment, constant worry and unrest, privation, overwork and exposure to life in narrow, difficult circumstances under which there is constant trouble to make ends meet. Meyer [23] observed that in many regions patients with involutional melancholia seem to come predominantly from the rural districts and suggested that this incidence is related to the narrower mental horizon in these districts. Henderson and Gillespie noted the same occurrence regarding much of their material in Scotland, where the struggle to gain an existence from the stubborn soil induces a particular kind of psychologic pattern.

Lewis [24] came to certain conclusions concerning the sixty-one "depressive states" which he studied, many of which were illuminating and controversial as regards the character of the psychotic depression.

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20. Courtney, J. W.: "Involutional" as Applied to Involutional Melancholia, Boston M. & S. J. **174**:416 (March 23) 1916.

21. MacCurdy, J. T.: The Psychology of Emotion, New York, Harcourt, Brace & Company, 1925.

22. Graves, W. P.: Textbook of Gynecology, ed. 4, Philadelphia, W. B. Saunders Company, 1928, pp. 38-39.

23. Meyer, A.: Inter-Relations of the Domain of Neuropsychiatry, Arch. Neurol. & Psychiat. **8**:111 (Aug.) 1922.

24. Lewis, A. J.: Melancholia: A Historical Review, J. Ment. Sc. **80**:1 (Jan.) 1934.

He found a paranoid content and compulsive symptoms and character traits in a high percentage of his patients, which is in harmony with the observations in our group. The great symbolic value of the life transitions incident to the period of involution emerges in the psychosis again and again and has been thoroughly discussed by MacCurdy,[21] Henderson and Gillespie [7] and others. Death, poverty, impending impotence, and the like, all have a profound, and often overwhelming, influence on the psyche of an adverse nature, in most instances far beyond the degree warranted by the facts.

The contributions of the psychoanalytic school, which have deepened understanding of the psychologic structure of melancholia in general, are of great value. In accordance with these, involutional melancholia is essentially a narcissistic disorder. Freud's [25] classic paper on melancholia is the basis for all later contributions. The amplifications of Abraham and Radó are fundamental. Regression takes place from the adult realistic regimen of the ego toward the infantile regimen of primary narcissism. In the illness there is a narcissistic wound which occasions genital loss as well as relinquishment of all adult realistic strivings. The failure to reach the adult goal means giving up the struggle and turning to the loving parent. The inevitable component of this regression is liberation of the earlier instinctive drives, oral sadistic impulses.[26] If one accepts the concept of obsessional character as a strong reaction formation against repressed anal tendencies, this is really understandable. Probably the anal tendencies are especially pronounced in this illness. The histories in our cases supply abundant evidence of the presence of this early character structure. Gerö,[27] in a recent contribution, expressed the belief that in the severe psychoneurotic depression the obsessional character is utilized by the ego in defense against therapy. The role of the ego in melancholia is sadistic, or, rather, the ego allows the conscience (superego) to torture it because of the guilty withdrawal to narcissistic isolation.[28] The outer world is given up. Love objects are lost and recreated in the ego, and then treated by the ego in a sadistic way.[29] There is a tremendous decrease in self esteem.

25. Freud, S.: Mourning and Melancholia, in Collected Papers, London, Hogarth Press, 1925, vol. 4, p. 152.

26. Abraham, K.: Notes on the Psychoanalytic Investigation and Treatment of Manic-Depressive Insanity and Allied Conditions, in Jones, E.: Selected Papers on Psychoanalysis, London, Hogarth Press, 1911, chap. 6, p. 137.

27. Gerö, G.: The Construction of Depression, Internat. J. Psycho-Analysis **17**:423 (Oct.) 1936.

28. (*a*) Federn, P.: Reality of Death Instinct in Melancholia, Psychoanalyt. Rev. **19**:129 (April) 1932. (*b*) Schilder, P.: Psychogenic Depression and Melancholia, ibid. **20**:10 (Jan.) 1933.

29. Marui, K.: Process of Introjection in Melancholia, Internat. J. Psycho-Analysis **16**:49 (Jan.) 1935.

The ego regards the superego as a separate torturing entity and asks in bewilderment the meaning of the suffering. (Some of the patients reported on by Henderson and Gillespie cried out, demanding to know why they let themselves suffer as they did, why they cried out.) The tension of the psychic sadism appears often to be transferred to the soma in the form of painful paresthesias, severe hypochondriacal complexes, etc. Suffering is peculiarly intense. The masochism of the patient increases the torment.[30] Alexander's [31] elucidation of the internecine strife between the ego and the superego in this psychologic state, in which the ego bribes the superego with suffering, is imperative for an understanding of the disorder. The harsh superego demands the most severe expiation before it will liberate the ego from punishment. The sadistic role of the superego also seems to be reflected in the severe disturbances of the body image, with the accompanying feelings of unreality which are so common in cases of involutional melancholia. Schilder [28b] investigated these disturbances in various psychoses and neuroses. Genital life is, of course, entirely lost in this melancholia, there being kept in mind the question raised by our study of the anamneses as to the degree to which these patients have ever successfully reached genitality. One must judge for oneself the extent to which the clinical facts bear out these theories, but we hope to show evidence for the underlying character disorder in this illness, its development in the psychosis and its exploitation by the psychosis itself.

We are familiar with the description of the obsessional character of the patient with compulsion neurosis, which has recently received new and enlightening analytic consideration by Gerö.[27] It is of historical interest that the same character type can be discerned in the anamneses in cases classified by Kraepelin as instances of "psychogenic depressions." The obsessional character is identifiable with the anal-erotic character, the distinguishing marks of which were first vividly outlined by Freud and later amplified by Jones [32] and Brill.[33] What Freud defined as the "cardinal triad" of this character type consisted of a group of reaction formations observed in the individual patient as excessive orderliness, parsimony and self willedness or obstinacy. Jones affirmed the close relation of these traits to narcissism and an exalted belief in

30. Radó, S.: Problem of Melancholia, Internat. J. Psycho-Analysis **9**:420 (Oct.) 1928.

31. Alexander, F.: The Psychoanalysis of the Total Personality, Nervous and Mental Disease Monograph 52, Washington, D. C., Nervous and Mental Disease Publishing Company, 1930.

32. Jones, E.: Collected Papers on Psychoanalysis, ed. 3, London, Baillière, Tindall & Cox, 1923.

33. Brill, A. A.: Studies in Abnormal Psychology, J. Abnorm. Psychol. **7**:302, 1915.

personal perfection. The odd paradox of the simultaneous appearance of striving for perfection and the narcissistic belief in its present grasp is observed in the obsessional character. The "perfectionist" has come to be a familiar type in the clinic. Sensitiveness to interference of any kind is a marked characteristic. Heavy-mindedness, dogged persistence and concentration, with a passion for thoroughness and completeness, round out the description. Brill was careful to point out the intimate relation of all these character tendencies to marked sadistic traits, with their masochistic counterparts.

Summary of Prepsychotic Personality Structure.—A careful inspection of the early life history of the patient with involutional melancholia shows that from childhood or puberty he has been an unusually guarded introvert, not even allowing himself the fantasied outlets of the freer, more harmoniously adjusted introvert. The patient with potential involutional melancholia has generally imposed a heavy burden on himself in the form of numerous restrictions on his instinctual life, has avoided pleasure as a goal to the point of fanaticism and has set up for himself a stern, unbending moral code, which no ordinary mortal could hope to satisfy. Pathologically inhibited, scrupulously meticulous about trifles, chronically worrisome, either justifiable or not, unable to free his affective forces for the uses of normally warm human relationships, he has guided his life firmly into a narrow, affectless road, which could at best only stifle the free play of personality. Rigidity is generally found to be of such pronounced degree that it not only shows itself in the psychic attitudes of the patient but is even transferred to the soma in the form of pathologic tensions and hypochondriacal disturbances of sensation. The psychotic phase is the culmination of a lifelong psychobiologic process of a distinct character; the pathologic markings are unique at each stage of the process. The outstanding characteristic (rigidity) of the personality drives the person into pathologic reaction formations at various stages of his career and prepares the way for the development of psychosis at the crucial era of transition into the late middle years.

COURSE AND PROGNOSIS IN RELATION TO PREDOMINANT PERSONALITY TRAITS

Attempts to determine the malignant nature of the disorder in the individual case have heretofore been based on evaluation of the content of the psychosis itself. No endeavor has been made, so far as is known, to judge the severity of the illness or the likelihood of recovery on the basis of the underlying personality and the psychopathologic manifestations in the history leading up to the illness. Briefly, study of the present series of patients tended to show that the degree of

"rigidity" manifested by the patient in his earlier life history largely determined the prognosis. The greater the rigidity of the personality in the prepsychotic phase the more malignant did the psychosis prove to be and the less hopeful the prognosis. Patients with the more plastic personalities tend to recover. Especially important in this series was the presence of a marked compulsive (psychasthenic) trend in the early history. When such was present the outcome was invariably bad. The outcome was worst of all in patients who had a history of outspoken compulsion neurosis. The patients with a previous compulsion neurosis showed in the psychosis the most marked agitation, overtalkativeness and hypochondriacal or somatic delusions and were chronically resistive to any kind of therapeutic approach. Nevertheless, blanketing in importance even the compulsive trend was the presence of the "narrowed horizon" as the chief characteristic of the syndrome of rigidity. When a history of pernicious, consistent narrowing of the mental horizon was present, with or without a history of compulsion neurosis, a malignant grade of psychosis invariably followed. The last finding appears to be the most signal fact in involutional melancholia.

Hoch and MacCurdy emphasized in their study of the psychosis that one can judge the malignancy of the disease by the presence or absence of certain symptoms in the psychosis. They classified the forms of the disease in two groups: the benign and the malignant. They expressed the belief that in the malignant form the presence of severe hypochondria is a general finding, to which they added peevishness and restriction of affect as complicating symptoms. In our patients, although hypochondria severe enough to be accompanied by somatic delusions of a bizarre type was often present in persons who did not recover, this symptom complex was not found to be a generally reliable indicator of the malignancy of the illness. Hoch and MacCurdy expressed the opinion that the benign form was characterized by marked emotional reaction, great anxiety and restlessness and prominent delusions of death and poverty. They contrasted this clinical picture with that of the malignant form, in which restriction of interest and affect was outstanding and frank fear was replaced by moaning, seclusiveness and insufficient depth of affect. The observations in our study did not bear out this distinction entirely. They tended to agree with the opinion that when restriction of interest is present the condition is malignant, but they did not bear out the statement that restriction of affect is a concomitant of malignancy. Many of the patients who did not recover preserved the chronic agitation and restlessness through the phase of psychosis until death or the time at which failure of recovery was recorded in the five year follow-up study. The patient with the most

severe psychosis in the whole group is still as agitated as at the time of admission. His radius of interest, however, has become increasingly reduced, until now he continues a constant circling within the sphere of a set group of hypochondriacal complexes. He has been ill for five years. Restriction of interest appears to be the malignant factor.

The data on the men may be analyzed more closely, in order to obtain exact figures for support of these contentions.

Of 25 men, 16 (64 per cent) failed to recover. Among these there were 9 deaths. One patient died as a result of general debility; 1, in delirium; 1, of pneumonia; 2, of infection, and 3, of natural causes; 1 committed suicide.

Of the 16 men who failed to recover, 9 had a history of previous obsessional character or of overt compulsive trends. The remaining 7 showed excessive restriction of the mental horizon at all points of their lives. All the men showed this restriction to a greater or less degree. Four with obsessional character in the group who recovered had the least severe psychosis; the psychosis was characterized more by chronic worrisomeness and penuriousness than by any ritualistic tendencies. Patients with the most severe disease were those with definitely ritualistic tendencies and overconsciousness, of the finicky, fussy sort.

Similar analysis of the women showed:

Of the 25 studied, 15 (60 per cent) failed to recover. This is impressive in view of the fact that there were no deaths or suicides. For 3 women no follow-up study was available. Of the women who did not recover, the personalities of 9 were characterized by an obsessional trend. In the total group 10 women showed an obsessional character, which means that only 1 with this type of character recovered. All the remaining 6 women who did not recover were characterized by the extreme restriction of horizon noted previously in the other patients.

All the women who recovered were found among the patients who showed the least pathologic prepsychotic personality. The only patients who showed any extroverted traits were among those who recovered. Two could be called slightly extroverted; 3 had no definite type of personality from the standpoint of general formulations; 1 was wrapped up in her business life and had sublimated well prior to onset of the psychosis, and another was a steady, conscientious worker, but had preveiously been fairly healthy.

Summary.—Of the 50 men and women patients, 31 (62 per cent) failed to recover. All these showed marked restriction of the mental horizon throughout life. Eighteen (60 per cent) of the 31 patients who did not recover showed classic "obsessional character," while only 5 (26 per cent) of the 19 who recovered showed obsessive traits. Four men with obsessional character among those who recovered must be regarded as having less severe disease; the psychosis was characterized more by chronic worrisomeness and penuriousness than by ritualistic tendencies. The 13 patients who did not recover were marked by extreme restriction of the mental horizon at all points of their lives, and all the patients showed restriction to a greater or less degree. Since involutional melancholia represents one phase in the development of a lifelong

biologic process, one is justified in drawing prognostic conclusions from an evaluation of the fixity of this biologic process in the prepsychotic stages.

CONTENT OF THE PSYCHOSIS AS RELATED TO PREPSYCHOTIC PERSONALITY

The role of the superego, or conscience, in this disease is peculiarly sadistic. In the psychoses of depression generally the superego may be regarded as taking on an even more punitive character than in normal life, but in involutional melancholia the role of punishment is more marked than in any other type of depression. One may conceive of this role as a horizontal line running from prepsychosis to psychosis, in which the punitive quality of the conscience becomes accentuated to the highest possible degree. The psychotic reaction formation consists merely in the partial emergence of the unconscious punitive agent into consciousness in the form of delusions of unworthiness and self-incriminating assertions of all sorts. General paranoid formations may be conceived on the same basis, accounting for the markedly high percentage of paranoid constructions in this psychosis, of which the observations in this study were confirmatory. In tracing by means of even briefer abstracts in each case the path of this horizontal line from prepsychosis to psychosis, the outstanding trend and its accompanying reaction became crystallized in a convincing manner. We could visualize the general tendency toward gradual restriction of the confines of the personality from prepsychosis to psychosis, with the emergence of the more pathologic attributes in isolated and heightened form. The psychosis appeared as a reproduction or highly magnified caricature of the pathologic life history.

In a careful analysis of the brief low power views of the various personalities of patients in whom involutional melancholia developed, certain aspects of the psychosis were sacrificed to tracing the course of the dominant trend of the personality and its culmination in the psychotic epoch. Extreme agitation and restlessness were obvious in every patient in whom apprehensiveness in any form was present. A dramatic psychomotor picture, with much pacing, wringing of hands, impulsive activity, screaming or overtalkativeness, was almost always the rule. In only 4 of the men and 3 of the women was there anything approaching a picture of retardation. Great anxiety, psychomotor restlessness, overtalkativeness with stereotyped apprehensive outbursts—these were the predominant features exhibited by the majority of the patients.

Mention has been made of the high proportion of patients in whom the paranoid element was present. To be exact, 13 of the men and 15 of the women showed definite paranoid trends with reference to other

persons in the environment. This is a finding which has not heretofore been emphasized in the literature regarding the clinical syndrome of involutional melancholia.

We have called attention elsewhere to the remarkable intellectual clarity which distinguishes the syndrome of involutional melancholia in the great proportion of patients. A patient who may evince bizarre somatic delusions and who entertains absurd ideas of death or poverty will answer all questions of orientation perfectly, whether spatial or temporal, and show flawless grasp of all details of his personal life, whether past or present. When confusion is present at all (it was noted in 4 women and 3 men), it concerns only the emotional issues involved; i. e., the patient is bewildered as to what he should "feel" about so-and-so; intellectual clarity as regards data of orientation remains unimpaired. In only 1 of the 50 patients studied was a degree of disorientation present; this man died in delirium.

A great deal of material has already been brought forth showing the high proportion of ideas of death and poverty and of religious delusions in patients with involutional melancholia. Mention has also been made of the large number of patients in whom autoerotic trends come to the surface. All these findings confirm the classic formulation of Kirby, Hoch and MacCurdy and others to the effect that ideas of death and poverty, religious delusions and autoerotic preoccupations are highly characteristic of the psychosis.

The case records here studied did not contain sufficiently detailed information from which to draw any accurate conclusions regarding certain other specific trends about which it would be desirable to know, such as the presence of feelings of unreality and obscene thought and ideation as a reaction formation in the psychosis, but a few patients manifested these trends. One or 2 expressed startling ideas showing fear of disruption of the body integrity; 1 patient feared that his body would be drawn and quartered and strung along the telephone poles of the main suburban highway. Later, he became convinced that this had happened. Such apprehensions regarding disruption of the body image are fascinating, and the psychosis in general would bear further investigation as regards the presence of such trends. They may often contain the key to the psychosis. Stärcke suggested that psychosis in general represents a fear of dismemberment. Tendencies toward castration fear are so symbolized.

Three of the men and 3 of the women had terrifying hallucinations, either visual or auditory, of a threatening moral nature. This observation confirms the distinct nature of hallucinations present in this psychosis.

IMPORTANCE OF THE PRECIPITATING SITUATION

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All the material properties in the external world which have a deep symbolic value for the psyche become the subjects of an obsessive anxiety. Money and sexual potency are special subjects. This accounts for the almost universal prevalence of delusions regarding these symbolic values in the psychosis. Feelings of unreality and fantasies of world destruction naturally follow. The delusional process is one of projecting onto the world responsibility for the altered feelings.

The unique precipitating situations which are found in almost every case of involutional melancholia have so far been investigated in only one study. Brew [35] who studied 50 cases, found the precipitating causes in women to be: psychic, in 42 per cent; somatic, in 38 per cent, and somatopsychic, in 20 per cent. The significant findings in many cases in which there was physical causation were closely bound up with psychic factors, i. e., the significance which the patient placed on the physical factor.

The material in our series confirmed strongly the conclusions drawn by Henderson and Gillespie, who found that in the men the precipitating factors were predominantly psychic (70 per cent) or somatopsychic, i. e., a combination of physical and psychic factors. In 57 per cent of

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severe psychosis in the whole group is still as agitated as at the time of admission. His radius of interest, however, has become increasingly reduced, until now he continues a constant circling within the sphere of a set group of hypochondriacal complexes. He has been ill for five years. Restriction of interest appears to be the malignant factor.

The data on the men may be analyzed more closely, in order to obtain exact figures for support of these contentions.

Of 25 men, 16 (64 per cent) failed to recover. Among these there were 9 deaths. One patient died as a result of general debility; 1, in delirium; 1, of pneumonia; 2, of infection, and 3, of natural causes; 1 committed suicide.

Of the 16 men who failed to recover, 9 had a history of previous obsessional character or of overt compulsive trends. The remaining 7 showed excessive restriction of the mental horizon at all points of their lives. All the men showed this restriction to a greater or less degree. Four with obsessional character in the group who recovered had the least severe psychosis; the psychosis was characterized more by chronic worrisomeness and penuriousness than by any ritualistic tendencies. Patients with the most severe disease were those with definitely ritualistic tendencies and overconsciousness, of the finicky, fussy sort.

Similar analysis of the women showed:

Of the 25 studied, 15 (60 per cent) failed to recover. This is impressive, in view of the fact that there were no deaths or suicides. For 3 women no follow-up study was available. Of the women who did not recover, the personalities of 9 were characterized by an obsessional trend. In the total group 10 women showed an obsessional character, which means that only 1 with this type of character recovered. All the remaining 6 women who did not recover were characterized by the extreme restriction of horizon noted previously in the other patients.

All the women who recovered were found among the patients who showed the least pathologic prepsychotic personality. The only patients who showed any extroverted traits were among those who recovered. Two could be called slightly extroverted; 3 had no definite type of personality from the standpoint of general formulations; 1 was wrapped up in her business life and had sublimated well prior to onset of the psychosis, and another was a steady, conscientious worker, but had preveiously been fairly healthy.

Summary.—Of the 50 men and women patients, 31 (62 per cent) failed to recover. All these showed marked restriction of the mental horizon throughout life. Eighteen (60 per cent) of the 31 patients who did not recover showed classic "obsessional character," while only 5 (26 per cent) of the 19 who recovered showed obsessive traits. Four men with obsessional character among those who recovered must be regarded as having less severe disease; the psychosis was characterized more by chronic worrisomeness and penuriousness than by ritualistic tendencies. The 13 patients who did not recover were marked by extreme restriction of the mental horizon at all points of their lives, and all the patients showed restriction to a greater or less degree. Since involutional melancholia represents one phase in the development of a lifelong

biologic process, one is justified in drawing prognostic conclusions from an evaluation of the fixity of this biologic process in the prepsychotic stages.

CONTENT OF THE PSYCHOSIS AS RELATED TO PREPSYCHOTIC PERSONALITY

The role of the superego, or conscience, in this disease is peculiarly sadistic. In the psychoses of depression generally the superego may be regarded as taking on an even more punitive character than in normal life, but in involutional melancholia the role of punishment is more marked than in any other type of depression. One may conceive of this role as a horizontal line running from prepsychosis to psychosis, in which the punitive quality of the conscience becomes accentuated to the highest possible degree. The psychotic reaction formation consists merely in the partial emergence of the unconscious punitive agent into consciousness in the form of delusions of unworthiness and self-incriminating assertions of all sorts. General paranoid formations may be conceived on the same basis, accounting for the markedly high percentage of paranoid constructions in this psychosis, of which the observations in this study were confirmatory. In tracing by means of even briefer abstracts in each case the path of this horizontal line from prepsychosis to psychosis, the outstanding trend and its accompanying reaction became crystallized in a convincing manner. We could visualize the general tendency toward gradual restriction of the confines of the personality from prepsychosis to psychosis, with the emergence of the more pathologic attributes in isolated and heightened form. The psychosis appeared as a reproduction or highly magnified caricature of the pathologic life history.

In a careful analysis of the brief low power views of the various personalities of patients in whom involutional melancholia developed, certain aspects of the psychosis were sacrificed to tracing the course of the dominant trend of the personality and its culmination in the psychotic epoch. Extreme agitation and restlessness were obvious in every patient in whom apprehensiveness in any form was present. A dramatic psychomotor picture, with much pacing, wringing of hands, impulsive activity, screaming or overtalkativeness, was almost always the rule. In only 4 of the men and 3 of the women was there anything approaching a picture of retardation. Great anxiety, psychomotor restlessness, overtalkativeness with stereotyped apprehensive outbursts—these were the predominant features exhibited by the majority of the patients.

Mention has been made of the high proportion of patients in whom the paranoid element was present. To be exact, 13 of the men and 15 of the women showed definite paranoid trends with reference to other

persons in the environment. This is a finding which has not heretofore been emphasized in the literature regarding the clinical syndrome of involutional melancholia.

We have called attention elsewhere to the remarkable intellectual clarity which distinguishes the syndrome of involutional melancholia in the great proportion of patients. A patient who may evince bizarre somatic delusions and who entertains absurd ideas of death or poverty will answer all questions of orientation perfectly, whether spatial or temporal, and show flawless grasp of all details of his personal life, whether past or present. When confusion is present at all (it was noted in 4 women and 3 men), it concerns only the emotional issues involved; i. e., the patient is bewildered as to what he should "feel" about so-and-so; intellectual clarity as regards data of orientation remains unimpaired. In only 1 of the 50 patients studied was a degree of disorientation present; this man died in delirium.

A great deal of material has already been brought forth showing the high proportion of ideas of death and poverty and of religious delusions in patients with involutional melancholia. Mention has also been made of the large number of patients in whom autoerotic trends come to the surface. All these findings confirm the classic formulation of Kirby, Hoch and MacCurdy and others to the effect that ideas of death and poverty, religious delusions and autoerotic preoccupations are highly characteristic of the psychosis.

The case records here studied did not contain sufficiently detailed information from which to draw any accurate conclusions regarding certain other specific trends about which it would be desirable to know, such as the presence of feelings of unreality and obscene thought and ideation as a reaction formation in the psychosis, but a few patients manifested these trends. One or 2 expressed startling ideas showing fear of disruption of the body integrity; 1 patient feared that his body would be drawn and quartered and strung along the telephone poles of the main suburban highway. Later, he became convinced that this had happened. Such apprehensions regarding disruption of the body image are fascinating, and the psychosis in general would bear further investigation as regards the presence of such trends. They may often contain the key to the psychosis. Stärcke suggested that psychosis in general represents a fear of dismemberment. Tendencies toward castration fear are so symbolized.

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the women they found that the situation was purely psychic. Physical factors were of importance in 21 per cent of the women and only 6 per cent of the men. The figures of Mabon [7] were not as striking; he found that in 47 per cent of his series (of both men and women) the situation was psychic, 34 per cent physical and in the remaining 17 per cent somatopsychic, a combination of the two.

Our findings were overwhelmingly confirmatory of the psychic nature of the majority of the precipitating situations. It may be added that in all the patients in whom a combination of psychic and physical (somatopsychic) factors played a role, the psychic factor was markedly in ascendancy. The figures are briefly as follows:

	Men, %	Women, %	Both Sexes, %
Psychic	72	64	68
Physical (somatic)	8	4	6
Somatopsychic	20	32	26

Of the men there were only 2 in whom direct physical disorder or trauma played a role; in 1 mild weakness or tremor of the arm prevented work; in the other pleurisy led to insidious hypochondria.

In analyzing more meticulously the precipitating situations for the men one may classify them as follows:

	No. of Men
Operation	1
Somatic disease (combined with psychic factors)	5
Psychic factors	
Drastic change in personal life (wife left patient, etc.) (in 2 combined with other factors)	3
Death of relative	2
Loss of money; financial or professional worry (in 2 combined with other factors)	5
Change of abode (in 1 combined with other factors)	2
Change in or giving up work (combined with other factors)	2
Fright or somatic illness	3
Insidious, obscure paranoid origin	2
Vague hypochondriacal origin	1
Specific guilt feeling	1

It is difficult to sort out factors of this kind, owing to the complex gradations in the mixture of various elements; nonetheless, in the situations in which psychic factors alone predominated these factors were uncomplicated by the presence of elements of other than a psychic nature. The prominent symbolic character of the psychic situations was self evident. They all, in some manner, constituted a threat to the integrity of the ego. Even when the factor was one involving concern about health, as in the case in which the psychosis was precipitated by failure to pass an insurance examination, it was the ego which fundamentally suffered rebuke. The patient fears that he cannot carry on with his ego strivings.

A vertical alinement of the precipitating factors in the women follows:

	No. of Women
Operation (combined with psychic factors)	3
Overt somatic disease (combined with psychic factors)	3
Accidents	1
Psychic factors	
Drastic change in personal life (combined with other factors)	5
Death of relative (in 2 combined with other factors)	3
Loss of money, property, etc. (in 1 combined with other factors)	3
Change of abode (in 2 combined with other factors)	3
Change in or giving up work	1
Vague hypochondriacal origin	2
Attributed to menopause (in 2 combined with other factors)	4
Onset with guilt feelings, specific or otherwise	2
Insidious paranoid origin (an adjunctive factor in 2)	3
Unexpected traumas, of unusual character	3

As for the men, the same general laws appear to hold true, namely, that patients with involutional melancholia break down in late middle life under trauma, chiefly of psychic origin and possessing a symbolic character with meaning for the psyche, which arouses latent anxiety regarding the future security of the ego. It is seen that in well over 50 per cent of both the men and the women the precipitating situation had a large, or wholly, psychic element and that this situation was a factor which struck deep into the patient's psychic life and undoubtedly played an important role in the development of the illness by virtue of the strong symbolic meaning latent in the incidents of the transitional years. A review of the entire life history of the patient with involutional melancholia results in the striking finding that the prepsychotic life shows stolid resistance to psychic traumas and absence of overt psychotic disorder; the previous troubles are more apt to be psychoneurotic.

Examination of the prodromal situations reveals the peculiar way in which the long-germinating precipitating situations suddenly undergo "flocculation." It was found that in nearly all patients, after irruption of the precipitating situation into the personal life, there was slow, gradual development of the psychosis in what may be called distinct stages. The comparatively long prodromal period has a tendency to culminate suddenly in a clinical picture of severe agitation, the ignition of which may be a fairly slight factor in the environment or the subjective psyche which symbolizes for the patient his inability to cope any longer with what he believes to be hostile forces, whether external or internal. The subjective factors appear to be as important as the objective in bringing the psychosis to full development. It seems that the lengthy period of incubation followed by a distinct stage of several months' duration in which the prodromal symptoms are gathering impetus offers remarkable opportunity for prophylaxis.

PREDICTABILITY OF THE PSYCHOTIC EPISODE

From the standpoint of prevention of the psychosis when malignant indications are present in the personality, or of forestalling a serious breakdown when the first trends are under way, it becomes of importance to the practitioner to know how great a period of leeway he has after the first manifestations of trouble are brought to his attention before the onset of serious psychosis. In other words, what, as a rule, is the "incubation period" of the psychosis, and on how long a period of grace may one count in endeavoring to interfere therapeutically? At what point does the breakdown begin, and when does it become obviously a psychosis?

Our study showed that in general there was a long incubation period before the full flowering of the psychosis, a period often extending over many months, or even years. Such a period would have been ample for interpolation by the practitioner who had access to the patient of sound guidance and general prophylaxis of a mental hygienic nature.

In practically all patients, after the irruption of the precipitating situation into the personal life, there was slow gradual development of the psychosis. One could witness the growth of the disease in much the same way as one does the development of a slow-growing neoplasm in an accessible part of the body.

For the men the intervals from appearance of the first signs to onset of the psychosis were as follows:

Interval	No. of Men
3 yr.	2
2 yr.	4
1 yr.	5
8 mo.	1
6 mo.	7
4 mo.	1
3 mo.	1
2 mo.	2
1 mo.	1

In all, there was the presence of increasingly malignant stages leading up to the final explosion into psychosis. In each patient, the psychosis was "predictable" and did not become clearly overt until the last minute, so to speak.

Even more striking were the intervals for the women.

Interval	No. of Women
7 yr.	1
5 yr.	1
4 yr.	1
2½ yr.	1
2 yr.	4
1 yr.	5
8 mo.	1
6 mo.	8
3 mo.	3

It is obvious that for the women, as for the men, there was a long period of incubation followed by a distinct stage in which the prodromal

symptoms were gathering impetus, with final precipitation of the overt psychosis only a few days prior to hospitalization, or within an even shorter time.

DISTINCTION BETWEEN MANIC-DEPRESSIVE PSYCHOSIS AND INVOLUTIONAL MELANCHOLIA

When the early history, life course and psychosis proper of the patient with involutional melancholia are examined and compared with those of the patient with manic-depressive psychosis, it is difficult to see how involutional melancholia came to be classified with manic-depressive psychosis. At no point, either in the prepsychotic history or in the psychosis itself, does the patient with involutional melancholia manifest classic manic-depressive symptoms or character traits. Even when one allows for the extent of ability to emphasize any psychosis, there is reason to believe that the "*Weltanschauung,*" or world outlook, of the patient with involutional melancholia differs markedly from that of the patient with manic-depressive psychosis. Clinical evidence for this is abundant. Perhaps the outstanding symptom complex in the patients considered in this study was "agitation" or "restlessness." In only 3 or 4 of 50 patients was there definite psychomotor retardation. Psychologically, this agitation may be considered as a belated and inhibited rebellion against the prolonged passive attitude toward life enforced for years by the harsh, intolerant, puritanical conscience. The forces of repression continue to hold sway in the psychosis, in the face of a final belligerent protest of the instinctive demands.

The classic concept of the prepsychotic personality of the manic-depressive patient, as formulated by numerous psychiatrists, such as Meyer, Hoch, Kirby and Bleuler, is one of labile mood swings, with the typical extroverted character, given to frank, open expression of feelings and opinions. A certain constitutional diathesis, defined by Kretschmer as "pyknic," has also been assigned to this character type. Whereas such categories cannot be followed too closely, it is noteworthy that in the 50 patients with manic-depressive psychosis whom we studied these characteristics predominated. No group of patients could be further from this general concept of the manic-depressive personality than the 50 patients with involutional melancholia. Introverted, markedly lacking in lability of mood, constitutionally of the asthenic type, the patient with involutional melancholia pursues a life course totally different in kind and character from that of the manic-depressive patient. Mention has been made of the failure of the patient with involutional melancholia to show a history of previous attacks of depression. This cannot be too greatly emphasized. The more or less easy "trigger threshold" of the manic-depressive patient, the comparative ease with which he is tipped into psychosis by a psychic or other agent—which many psychiatrists have come to believe is rooted in a subtle, as yet

undefined, constitutional factor—is lacking in the patient with involutional psychosis. As a matter of fact, the patient with involutional melancholia shows an extraordinary toughness or resistance to inroads of psychic and other trauma in his earlier life history. There is a similar difference in the character of the prodromal period in the two groups of patients. In the manic-depressive patient the psychosis may be precipitated almost instantaneously by a psychic or other circumstantial insult, the period of incubation being short and impossible to utilize for the purpose of forestalling psychosis. In the patient with involutional melancholia, on the other hand, one finds almost universally the presence of a long, slow-growing prodromal period, in which the careful observer may witness the psychosis larvating under his eyes and in which wise and tactful interference on the part of the psychiatrist may avert the outbreak of real psychosis. Lastly, there is the difference in the character of the psychosis itself. As has been emphasized elsewhere in this paper, the psychosis of involutional melancholia is characterized by depression without retardation. Anxiety with extreme agitation is marked. Psychomotor activity is increased, rather than reduced. Circumstantiality is lacking, and in its place is the tendency toward rigid stereotypy of anxious utterances of a self-accusatory, delusional nature. The paranoid element in the psychosis is marked. The same rigidity which is present in the earlier life history and distinguishes the psychobiologic process of this disease maintains full sway throughout the various deviations of the psychosis itself. Patients who recover fail to show anything even remotely suggestive of elation or satisfaction at having recovered and having been restored to normal life. The singularly poor prognosis (only 38 per cent of patients in our series recovered) as compared with that for manic-depressive psychosis is further evidence of dissimilarity of the two diseases.

SUMMARY

1. Critical examination of the total life pattern of 50 patients with involutional melancholia reveals a lifelong fundamental process, a reaction type in the Meyerian [36] sense, which bears characteristic stigmas from birth to death. Throughout the life history of the involutional patient runs a single biologic thread or process, which is best described by the word "rigidity." This rigidity characterizes chiefly the unconscious adaptive mechanisms which the patient has built up in order effectively to control the instinctual forces. "Control" is probably not an adequate word; something approaching the notion of strangulation would serve better.

36. Meyer, A.: Objective Psychology or Psychobiology with Subordination of the Medically Useless Contrast of Mental and Physical, J. A. M. A. **65**:860 (Sept. 4) 1915.

2. The predominant personality traits can be summarized as follows: Eighty per cent of the patients showed marked introversion; 62 per cent (72 per cent of the men and 52 per cent of the women), strong obsessional (compulsive) character; 74 per cent (80 per cent of the women and 68 per cent of the men), strong voluntary repression; 46 per cent (60 per cent of the men and 32 per cent of the women), sexual maladjustments; 50 per cent (48 per cent of the men and 52 per cent of the women), sadomasochistic traits, and 40 per cent (48 per cent of the men and 32 per cent of the women), hyperreligious trends.

3. Our study reveals abundant support for the contention that involutional melancholia is not to be classified, as the majority of psychiatrists now appear to do, as a subdivision or part of manic-depressive psychosis. Involutional melancholia is a distinct entity, with a prepsychotic history and a psychotic content which differentiate it from any other psychotic reaction.[37]

4. A study of the course and prognosis of the psychosis in relation to predominant personality traits reveals as the main finding that the degree of rigidity of the lifelong personality of each patient may justifiably be utilized by the clinician in judging the probable malignancy of the psychosis.

5. The study of the content of the psychosis as related to the prepsychotic personality reveals that in practically every patient a strong central thread, consisting chiefly of the repressive forces in the personality (superego, conscience), may be traced in its workings from prepsychosis to psychosis, the psychotic phase revealing exacerbation of the pathologic functioning of this agent in dramatic miniature. Reaction formations in the psychosis springing from the underlying personality trends are clearly visualized.

6. A study of precipitating situations reveals a high percentage of psychic factors and somatopsychic causes. In short, it is the trauma, possessing symbolic character with meaning for the psyche, that arouses latent anxiety with regard to the future security of the ego.

7. The illness has a high degree of predictability in the long prodromal era. The involutional process tends to crystallize only at the last minute, under the impact of an added trauma (usually of a psychic nature). The magnitude of this extensive prodromal stage is obvious from the following statistics:

1 to 3 years	11 men	1 month to 1 year	12 men
1 to 3 years	13 women	3 months to 1 year	14 women
	24 (48%)		26 (52%)

37. Meyer, A., and Dana, C.: A Discussion on the Classification of the Melancholias, J. Nerv. & Ment. Dis. **32**:114, 1905.

8. The frequent appearance of paranoid trends has not been sufficiently emphasized in the literature on involutional melancholia. Twenty-eight patients (56 per cent) showed the presence of definite paranoid trends in relation to persons in the environment. This high incidence leads one to consider this delusional formation as one of the characteristics of the disease. The presence or absence of paranoid trends in the content of the psychosis seems to bear only slight relation to the prognosis. Of patients for whom data are complete, 46 per cent showing paranoid trends recovered or made marked improvement, while 54 per cent failed to recover.

9. The age of onset in relation to prognosis is of interest. The highest incidence in women (80 per cent) was in the age group of from 40 to 60. The highest incidence in men (68 per cent) was in the age group of from 50 to 70. The general concept of an unfavorable prognosis for men over 50 and for women over 45 years is further substantiated by our findings.

Age of Onset, Yr.	Patients Recovered, Percentage
30–40	50
40–50	55
50–60	20
60–70	10

10. General inadequacy in the sphere of sexual life was noted in both men and women. The majority of men (22) who were married showed definitely inadequate sexual adjustment. In unmarried men homosexual trends were outstanding. Only 15 of the 25 women were married, and 7 were poorly adjusted to the marital situation. The relation of the marital situation to prognosis is expressed numerically as follows:

	Men	No. Recovered	Women	No. Recovered
Married				
Moderately well adjusted	10	3 (33.3%)	7	7 (100%)
Poorly adjusted	12	2 (16.6%)	7	0
Unmarried	3	0	10	2 (20%)

All patients who had children and whose relation to them was good were found in the group who recovered. It seems that the harmonizing and balancing influence of normal family life tends to decrease the malignancy of the psychotic episode. Such an expression represents to some degree an imponderable factor, as these relationships are dependent on the soundness of the personality.

11. The retention of intellectual clarity is worthy of mention. When confusion is present at all, it concerns only the emotional issues involved. Data of orientation remain unimpaired.

Case Reports

ATHETOSIS AND PALLIDAL DEFICIENCY

J. W. Papez, M.D., Ithaca, N. Y.; J. Hertzman, M.D., Cincinnati, and R. W. Rundles, B.A., Ithaca, N. Y.

This report concerns a case of athetoid paralysis in a woman who, in spite of a severe motor handicap, attained a high degree of cultural development. The brain stem of this patient has been studied in detail. Because of the specific nature of the lesion and its theoretic bearing on the organization of the extrapyramidal motor system, the details of this case are placed on record.

REPORT OF A CASE

History.—H. G. D., a woman aged 35, who died of bronchopneumonia and other complications, was born on February 21, 1900, in Richmond, Ind. Weight at birth was 6 pounds and 12 ounces (3,062 Gm.). She was the first child; labor was precipitate, lasting fifteen minutes. No instruments, chloroform or ether was used. The infant appeared normal and nursed. The mother had a retained afterbirth and on the eleventh day exhibited toxic and delirious symptoms. She was given bromides, but the infant was allowed to nurse. On the following day the babe became somnolent and remained so for forty-eight hours. Afterward, the parents expressed the belief that the drug was the cause of the athetoid paralysis which became manifest as the child grew up.

During the first year of life the infant had no illness except an occasional cold. The earliest symptoms of paralysis observed were general muscular weakness. For several years the child developed poorly. The neck seemed weak, and until she reached her teens it was with difficulty that she could hold up her head. Until she was 5 years old she could not sit alone on the floor unless propped up with pillows. She did not walk until the age of 7 and then not well. At the age of 13 she walked upstairs by herself for the first time.

Owing to incoordinate movements of the hands, head and mouth, the patient was always unable to feed herself. It was practically impossible for her to use a pen or pencil. She did all her writing on a typewriter by using the right index finger and steadying the wrist with the left hand. In the last few years of life she talked plainer and walked a little better, though always with great impediment.

She began to talk after the age of 4, but with difficulty. Speech was hesitant and slurred, and she was always unable to articulate properly. She choked readily and had to be fed carefully. This was due to the athetoid condition and poor voluntary control of the muscles of the mouth and throat.

From the Department of Anatomy, the Cornell University Medical College (Drs. Papez and Mr. Rundles), and the Longview State Hospital (Dr. Hertzman).

Drs. E. A. Baber and J. F. Bateman, of the Longview State Hospital, gave us the opportunity to report this case.

The ocular muscles alone of the entire body musculature were not involved. All movements of the eyes, the pupillary reflexes and the functions of accommodation were normal.

Visual, acoustic and other receptive functions were not affected in any noticeable way, which made possible the development of her psychologic functions to a remarkable degree. During childhood, her mother read to her many books and magazines, taught her music, etc. Perceptual functions and comprehension were keen. She learned to read to herself at the age of 7. The Bible, dictionary and music book were the chief sources of discipline. She did not use regular school books. She had a wonderful memory and could recall the date and details of any past incident of note.

In all her motor performances she was self trained, as no one could help her in this respect. She could not go to school. In spite of her great physical disability, she taught herself to do minor household duties, and especially to use the typewriter. With perseverance, she was able to write prose and verse and to compose music. She wrote stories, articles, sermons and Christmas messages for various papers. She was a good song critic. She composed and arranged many songs of her own and set to music some for other authors.

Physically, she was underdeveloped and always thin. Her height was about 5 feet and 4 inches (162 cm.), and her weight did not exceed 85 pounds (38.6 Kg.). She was chronically constipated. Menstruation began at the proper age, and the periods were regular, varying only at times when she was more nervous than usual. She had measles, chickenpox, whooping cough, smallpox, mumps and several bad colds. These did not materially affect the athetoid condition, which remained about the same throughout life.

Emotionally, she was well balanced. Her family was able to provide an environment conducive to her intellectual development and to a favorable social adjustment. She had a happy, cheerful disposition, was sociable and made many friends. Although she was sensitive about her physical condition, she made every effort to overcome this feeling. She was ambitious. She tried hard to adapt herself to the conditions and determined to develop her residual capacities. Her many accomplishments were the result of this determination.

In 1935 the financial affairs of the family became acute. This economic difficulty and disappointment due to postponement of her proposed marriage caused the patient to become very depressed. She refused to eat, expressed various delusions of infidelity and finally became such a burden at home that it was necessary for her to be probated to the Longview State Hospital. The condition was diagnosed as a situationally reactive depression of the psychoneurotic type, complicated by a severe bronchial infection.

Family History.—The parental history on both sides was medically without significance. The mother, who had taken care of the patient up to the time of admission to the hospital, broke down soon afterward and was admitted to the Longview State Hospital, suffering from a manic-depressive psychosis.

Physical Examination.—This was made by one of us (J. H.) on Oct. 24, 1935. The patient was admitted to the hospital in an agitated condition and was carried in on a stretcher. She was markedly undernourished and emaciated and was reduced to the appearance of skin and bones. Her hair was black. The skin was thin, dry, inelastic and pale. There was no dyspnea, icterus or cyanosis. The temperature was 98 F., the pulse rate 108, the respiratory rate 20 and the blood pressure 104 systolic and 70 diastolic. A severe bronchial cough was present on her admission to the hospital. Wassermann and other laboratory tests gave normal results.

The face was markedly shrunken. The nose, ears and eyes were normal. The pupils were of medium size, equal, round and regular and reacted well to light and, presumably, in accommodation. The movements of the eyes were normal. The conjunctivas were pale. There was no lag or tremor of the lids and no nystagmus or exophthalmos. Examination of the fundi showed that the disks were well outlined; the central vessels and the retina appeared normal. There was no enlargmeent of the lymph glands of the neck or of the thyroid. Examination of the lungs, heart and abdomen revealed nothing of note.

The mucous membrane of the mouth, fauces, palate and pharynx was markedly injected, dry and cracked. There were no teeth in the lower jaw. Most of the teeth were present in the upper jaw, and there were pyorrhea and a calculous

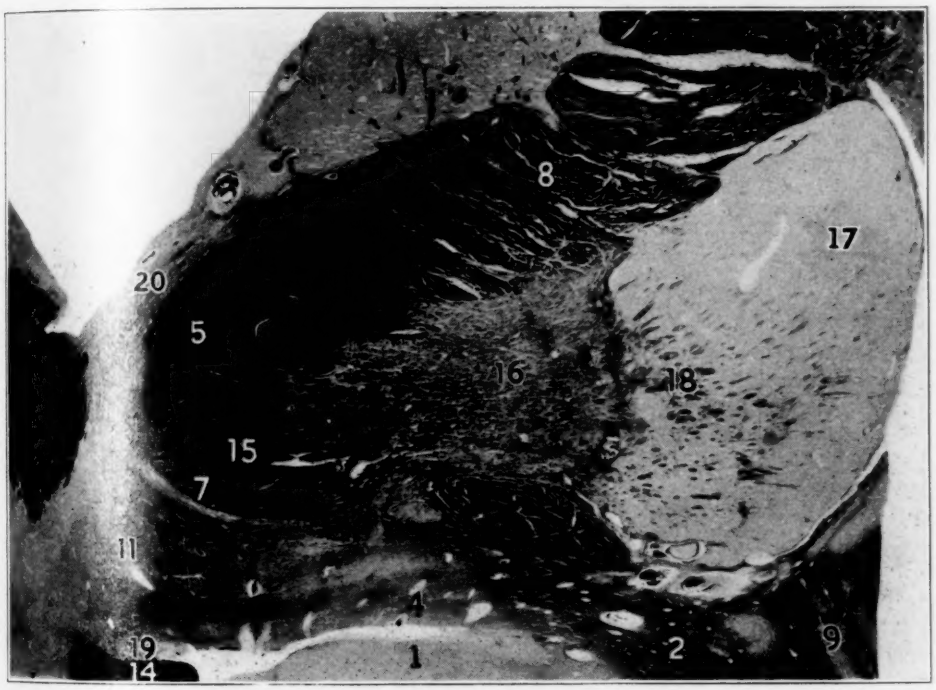

Fig. 1.—Section through the anterior part of the corpus striatum and the anterior limb of the internal capsule.

In this figure and in the accompanying figure, the following abbreviations are used: *1* indicates the amygdala; *2*, the amygdalar tract; *3*, the anterior commissure; *4*, the anterior perforated substance; *5*, the anterior thalamic radiation; *7*, the inferior thalamic peduncle; *8*, the internal capsule; *9*, the lateral olfactory nuclei; *10*, the mamillary body; *11*, the medial bundle of the forebrain; *12*, the medial nucleus of the thalamus; *13*, the medullary stria; *14*, the optic tract; *15*, the pallidal efferent fibers; *16*, the pallidum; *17*, the striatum; *18*, the striopallidal fibers; *19*, the supraoptic nucleus; *20*, the terminal stria; *21*, the uncinate fasciculus, and *22*, the ventral anterior nucleus. The fornix appears at the extreme left.

deposit around the teeth. The teeth and hard palate were covered by a thick, tenacious yellow exudate. The tongue was somewhat irregular. The palatal and pharyngeal reflexes were active, showing no flaccid paralysis.

Neurologic Examination.—The entire body exhibited an athetoid posture. As the patient was seen lying in bed, the extremities had a spastic attitude, and there was marked contracture of the right wrist. Any attempt at movement of any muscle group in the body was characterized by a marked overflow in all the neighboring muscles, which resulted in spastic athetosis and inability to perform coordinated movements. These movements were of a markedly choreiform and athetoid nature. This explosive overflow was apparent in every muscle in the body, including those of the face, jaws and the muscles concerned with swallowing and speech. The movements of the eyes were the only exception.

The peculiar overflow and athetoid movements were especially noticeable in the face. Drooling was present. When the patient attempted to speak, the mouth opened wide, and she could not close it until she was able to relax the muscles by prolonged voluntary effort. Apparently, she was able to employ relaxation as a control of the overflow. She opened the mouth and closed it with difficulty until she was able to relax the various spastic groups. When she opened her mouth it assumed a spastic, grotesque form. Speech was described as labored, slurred and guttural. At the time of examination the patient was agitated, and speech could not be carried out. When she attempted to swallow or talk the muscles of the face made peculiar grimaces, and the spastic overflow into the bodily musculature produced bizarre movements.

The muscles of the limbs were shrunken and unbalanced. On voluntary effort they showed spasticity and athetoid movements. These choreiform movements were prominent in all activities. The patient, however, was able voluntarily to move the arms, legs, head, neck and body in a markedly athetoid and incoordinated way. When she attempted to do something the overflow set in, but she was able to relax and to perform the movement slowly. The paralysis and overflow were most severe in the right upper extremity. When she attempted to move quickly the overflow into the associated groups of muscles was so marked that all the muscles exhibited marked spasticity and athetosis. This hyperkinesis involved the entire body and was present in any attempt to move the arms, fingers, legs or body, to talk or to swallow. Spastic atrophy and unbalance were noted in every muscle of the body, including the muscles of the spine. At the time of examination, she had been in bed for two months, and the muscular agitation was probably more marked than usual, owing to her excited state.

Examination of sensibilities could not be made; presumably, they were normal. No sensory disturbances were noted.

The reflexes were hard to test. The biceps and triceps reflexes were present on both sides, but a little more active on the right. The abdominal reflexes were equal on the two sides and hyperactive. The right knee jerk was a little more active than the left. There was no ankle or patellar clonus. Chaddock, Gordon and Babinski reflexes were present on the right side but not on the left.

Summary.—The patient presented a classic picture of bilateral atrophic dystonic athetoid paralysis, such as is commonly considered to be due to injury of the brain at birth. Most of the muscular symptoms were referable to derangement of the extrapyramidal motor system. The presence of a Babinski sign and other abnormal reflexes on the right side indicated an injury to the pyramidal tract arising from the left hemisphere. The muscular incoordination, the lack of synergic control of reciprocal muscular groups, the overflow, the tonic innervation and the athetosis were interpreted as due to a lesion of the corpus striatum.

Course of Illness.—The terminal history of the patient was that of an acute illness. On admission there was a severe bronchial cough. This became progressively worse, and signs of pulmonary congestion or bronchopneumonia

developed. Emaciation and inanition became extreme. Fluids were administered by vein and rectum and hypodermically. The patient rapidly reached exhaustion and died seventeen days after entering the hospital.

Autopsy (Dr. Douglas Goldman).—The organs showed many signs of an acute infection. The cause of death and the anatomic diagnosis were given as bronchopneumonia, fibrinous pleuritis, pyelonephritis, cystitis and chronic appendicitis.

The brain weighed 1,300 Gm. and was normal in external appearance. The cerebral vessels seemed normal. The hypophysis cerebri showed no gross pathologic changes. The tip of the right temporal lobe was adherent to the dura. The

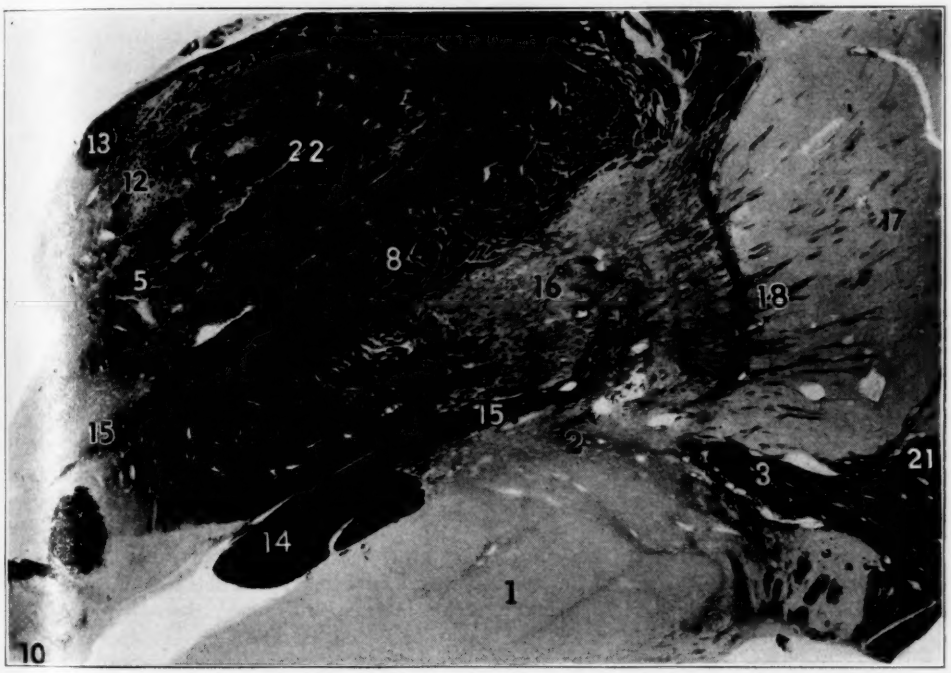

Fig. 2.—Section through the level of the mamillary body and the anterior part of the thalamus. The pallidum (*16*) and the pallidal efferent fibers (*15*) appear markedly reduced in this figure.

meninges showed definite areas of scarring over the base, in the region of the middle temporal fossae. The brain was preserved in a dilute solution of formaldehyde and later shipped to the Cornell University Medical College for detailed study.

The following observations were made by one of us (J. W. P.): There was almost complete absence bilaterally of the small lenticulostriate arteries, which normally arise from the first portion of the middle cerebral artery. Either the arteries had been pulled out at birth or, owing to other causes, had failed to develop in sufficient number. These arteries normally supply the globus pallidus. The small basal branches of the anterior cerebral arteries were present, but were fewer than usual. The insular region was small on both sides, except for its

anterior gyrus, which was prominent bilaterally. This condition indicated reduction of the corpus striatum, which was most evident on the left side.

The caudate nuclei showed a number of radiating, stripelike depressions. The left caudate nucleus appeared somewhat reduced. Except for the stripes, the ependymal surfaces of the caudate nuclei appeared smooth, showing no evidence of ventricular disease.

The cerebral cortex was normal, except for the changes noted and the small scar on the under surface of the right temporal lobe. The brain was well preserved, and the cortical configuration conformed to the normal.

After the brain was photographed, the brain stem, including the corpus striatum and the olfactory region on both sides, was separated from the cortex by circular incisions around the insulae. Most of the cerebellar cortex was trimmed down to the basal cerebellar nuclei. The brain stem was photographed, mordanted in a 3 per cent solution of potassium bichromate for a number of weeks and infiltrated and blocked in pyroxylin. The brain stem was cut in serial sections, each 40 microns thick. Every fifth section was stained by a modification of the Weigert-Pal method, and every tenth corresponding section was stained for cells with cresyl violet. Both series were complete, and the staining (done by one of us, [R. W. R.]) was good.

Microscopic Examination.—The sections showed remarkable absence of cells in the globus pallidus of both sides. The usual lenticulostriate arteries which perforate the sublenticular region were notably deficient in number. The deficiency in number of the pallidal cells was estimated to be 75 per cent or more. There was practically no perivascular infiltration or evidence of recent chromatolytic changes in this region or elsewhere. The condition of cellular deficiency in the pallidum affected the medial and lateral segments of both sides. The cells of the nucleus basalis were normal.

The efferent pallidal tracts showed a corresponding reduction bilaterally. These fibers stained darkly as they shifted through the basis pedunculi. The fasciculus lenticularis and the ansa lenticularis passed in the subthalamus toward the red nucleus. They were markedly reduced. The pallidohypothalamic tract, passing over the fornix into the tuber cinereum, was also reduced. The pallidosubthalamic fibers, passing to the subthalamic nucleus of Luys, were reduced. The pallidomesencephalic fibers to the interstitial nucleus and the pallidotegemetal tract could not be identified with certainty. The general picture was that of severe deficiency of pallidal cells and of all the pallidal efferent fibers. This deficiency appeared a little more severe on the left side.

The cells and descending fiber connections of the red nucleus and the subthalamic nucleus were normal on both sides. There was noticeable reduction of fibers to these nuclei from the pallidum.

There appeared to be marked reduction of fibers of the lateral pontile fasciculi as they passed down in the lateral region of the substantia nigra. Aside from this, the midbrain and tegmental structures were normal.

The caudate nucleus and the putamen on both sides were nearly normal. As usual, numerous small cells and the sparse large cells were present. Afferent connections to the corpus striatum, which may come from the thalamus, notably, in the inferior thalamic peduncle (ansa peduncularis), the anterior thalamic peduncle and the thalamic radiations from the ventral and lateral thalamic nuclei, appeared normal.

The efferent fibers of the striatum (caudate nucleus and putamen) were numerous and of nearly normal volume. These fibers gave the brown reaction which they often show in Weigert sections. On account of this peculiar light

yellow or brown coloration, they could be traced readily through the pallidal segments, through the cerebral peduncles and into the substantia nigra.

In these preparations, it was clearly demonstrated that the fibers which arose from the caudate nucleus and the putamen converged in several ways on the pallidum, which they entered and traversed. Part of the fibers appeared to end in the pallidum and to provide some of the terminal neuropil seen in both its segments. Others traversed the pallidum and entered the cerebral peduncles, within which they gradually shifted as lightly stained bundles, and finally rose dorsally to enter and end in the substantia nigra. These efferent striatal fibers can be accurately designated as striopallidal and strionigric. None of these fibers were contributed to the ansa or the fasciculus lenticularis or to other pallidal efferent tracts. The striopallidal and strionigric fibers constituted a fiber system entirely separate from the pallidal efferent tracts. Their ultimate destinations were the pallidum and the substantia nigra.

The pyramidal tracts at the level of the medulla oblongata were of normal size, but there was slight reduction of the left half of the medulla, indicating diminution of some structures on that side. The lateral pontile fasciculi, which in normal specimens traverse the lateral part of the substantia nigra and shift dorsally through the medial lemniscus toward the masticator nucleus, were markedly deficient on both sides. Whether this was due to deficiency of cortical or pallidal fibers could not be determined.

All the other regions of the brain stem, such as the olfactory region, septum, hypothalamus, dorsal thalamus, internal capsule, midbrain, tegmentum, pons, cerebellum and medulla oblongata, appeared normal. Excessive masses of pigment were observed in the cells of most nuclei.

Except for the deficiency in the pallidum and its connections already noted, the other components of the extrapyramidal motor system were present and well developed.

COMMENT

This case, on account of bilateral and sharply localized deficiency of the pallidum and its efferent tracts, sheds light on the nature of the functions which the pallidum contributes to motor performance. It is evident that coordination, the topical and reciprocal innervation of muscular groups under voluntary innervation, was grossly disturbed. This condition may be described as a disturbance of synergy. To understand this, the concept of a totally integrated motor apparatus is necessary.

In recent years it has become apparent that motor performances are the products of integration of the activities of various central levels, notably, the cerebral cortex, corpus striatum, tegmentum, cerebellum, vestibular centers and spinal cord.[1] The well defined fiber connections which exist between these levels make such an integration of function indispensable. No anatomic, physiologic or clinical interpretation of the motor performance is possible without a consideration of this entire nexus. Although each level contributes its own physiologic potentials to the total process, it cannot function in its proper capacity without circuiting through the other levels.[2]

1. Cobb, S.: Motor Integration and Locomotion, in a Preface to Nervous Disease, Baltimore, William Wood & Company, 1936, chap. 3, pp. 35-59.

2. Papez, J. W.: The Brain Considered as an Organ: Neural Systems and Central Levels of Organization, Am. J. Psychol. **49**:217-232, 1937.

From comparative and experimental neurology, it is known that the central motor apparatus arises as an autogenous system [3] and is further developed on a reflex plane,[4] including the vagal, trigeminal, vestibular, tectal, tegmental [5] and hypothalamic reflexes.[6] The median portion of the cerebellum is usually an accessory structure which reenforces these reflex functions.[7] In lower animals the activities of these reflex components are combined in a complex manner and may be well maintained, although poorly adjusted, even in the absence of the forebrain.[6]

In all the higher forms (reptiles, birds and mammals) encephalization of this involuntary apparatus takes place, first, by the elaboration of the corpus striatum [8] and, second, by the addition of the cerebral cortex and the lateral lobes of the cerebellum.[7] In man encephalization, with the increase in the voluntary functions, has attained a high degree of dominance over the lower apparatus.[9] The involuntary processes of the lower levels are merged with those of the cortex and corpus striatum and in many phases of activity have lost much of their independence.

This upward shift of functional dominance is well illustrated in the higher mammals. In the cat or dog the entire cerebrum, including both the corpora striata, may be removed without producing paralysis of the lower motor apparatus.[9] On the contrary, in the human subject large lesions of the motor cortical areas or of the corpora striata usually produce gross motor deficiencies.[10] Unilateral lesions may be well compensated,[11] but bilateral lesions, even when congenital, impose a severe handicap on the patient.

The old belief is still current that the pyramidal tracts are the main pathways of the voluntary impulses which leave the cortex for the lower levels. Much of the older clinical diagnosis was based on this concept of an upper motor neuron.[12] With advance of knowledge, the

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3. Coghill, G. E.: The Early Development of Behavior in Amblystoma and in Man, Arch. Neurol. & Psychiat. **21**:989-1009 (May) 1929.

4. Sherrington, C. S.: The Integrative Action of the Nervous System, New Haven, Conn., Yale University Press, 1923, pp. 1-411.

5. Magnus, R.: Physiology of Posture, Lancet **2**:531-536 and 585-588, 1926.

6. Bard, P., and Rioch, D. M.: A Study of Four Cats Deprived of Neocortex and Additional Portions of the Forebrain, Bull. Johns Hopkins Hosp. **60**:75-148, 1937.

7. Brouwer, B.: Anatomical, Phylogenetical and Clinical Studies on the Central Nervous System, Herter Lectures of the Johns Hopkins University, Baltimore, Williams & Wilkins Company, 1927, vol. 17, pp. 45-63.

8. Ariëns Kappers, C. U.: The Corpus Striatum: Its Phylogenetic and Ontogenetic Development and Functions, Acta psychiat. et neurol. **3**:93-113, 1928.

9. Fulton, J. F., and Keller A. D.: The Sign of Babinski: A Study of the Evolution of Cortical Dominance in Primates, Springfield, Ill., Charles C. Thomas, Publisher, 1932, pp. 120-139.

10. Foerster, O.: The Motor Cortex in the Light of Hughlings Jackson's Doctrines, Brain **59**:135-159, 1936.

11. Dandy, W. E.: Physiological Studies Following Extirpation of the Right Cerebral Hemisphere in Man, Bull. Johns Hopkins Hosp. **53**:31-51, 1933.

12. Gowers, W. R.: A Manual of Diseases of the Nervous System, ed. 2, Philadelphia, P. Blakiston, Son & Co., 1892.

rubrospinal tracts and other tegmental structures headed by the corpora striata were added as a subcortical extrapyramidal system.[13] More recently, the extrapyramidal zones of the cerebral cortex and their efferent fibers have been recognized as the chief sources of cortical innervation of the extrapyramidal system, passing mainly to the lateral lobes of the cerebellum and thence to the corpora striata.[10] It now seems probable that the voluntary processes leave the cortex by the extrapyramidal as well as the pyramidal pathways,[14] as suggested by Sir Victor Horsley.[14a]

The psychologically determined course of an act is cortical in nature and can be readily recognized as a conscious process.[15] It is evident that this voluntary flux was normal in the present case. The handicap to the voluntary performance was distinctly subcortical, interfering with the proper execution of synergies and coordinated movements. It may be inferred that the motor area and the premotor and other extrapyramidal areas providing the outlets for the voluntary processes were nearly normal.

The corpus striatum forms an important link in the topical organization of the subcortical motor pathways. It is likely that it is afferented not directly from the cortex, but indirectly, by the brachium conjunctivum, the medial lemniscus and other afferent pathways which reach it through the dorsal thalamus. In the present case these afferent connections appeared normal, so that the dysfunction may be attributed to the pallidal deficiency.

Diseases and agenesis of the corpus striatum have been studied by various authors, including Wilson,[13] the Vogts,[16] Jacob,[17] Hunt,[18] Foix and Nicolesco,[19] Morgan [20] and others. The association of juvenile athetoid paralysis with lesions of the corpus striatum has been reported

13. Wilson, S. A. K.: Progressive Lenticular Degeneration: A Familial Disease Associated with Cirrhosis of the Liver, Brain **34**:295-509, 1912.

14. Fulton, J. F.: The Interrelation of the Cerebrum and Cerebellum in the Regulation of Somatic and Autonomic Functions, Medicine **15**:247-305, 1936.

14a. Horsley, V.: The Linacre Lecture on the Function of the So-Called Motor Area of the Brain, Brit. M. J. **2**:125-132, 1909. Bucy, P. C., and Case, T. J.: Athetosis: II. Surgical Treatment of Unilateral Athetosis, Arch. Neurol. & Psychiat. **37**:983-1020 (May) 1937.

15. Bentley, M.: The New Field of Psychology: The Psychological Aspects of Action, New York, D. Appleton-Century Company, Inc., 1934, chap. 6, pp. 209-231.

16. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen des striären Systems, J. f. Psychol. u. Neurol. **25**:627-846, 1920; abstracted, Arch. Neurol. & Psychiat. **10**:563-583 (Nov.) 1923.

17. Jacob, A.: Die extrapyramidalen Erkrankungen, Berlin, Julius Springer, 1923, pp. 1-419; Anatomy, Clinical Syndromes and Physiology of the Extrapyramidal System, Arch. Neurol. & Psychiat. **13**:596-620 (May) 1925.

18. Hunt, J. R.: Progressive Atrophy of the Globus Pallidus, Brain **40**:58-148, 1917.

19. Foix, C., and Nicolesco, J.: Anatomie cérébrale. Les noyaux gris centraux et la région mésencéphalo-sous-optique, Paris, Masson & Cie, 1925.

20. Morgan, L. O.: The Corpus Striatum, Arch. Neurol. & Psychiat. **18**:495-549 (Oct.) 1927.

in a sufficient number of cases to be significant. More extensive lesions are common. The motor and premotor areas and other regions of the cortex may be affected. The substantia nigra, the red nucleus, the pontile and cerebellar connections and the pyramidal tract may be involved. Whenever sizable lesions occur in the motor apparatus, some form of motor disability occurs.

In this case the lesion was sharply localized bilaterally in the pallidum. There was marked and almost equal reduction in the number of pallidal cells and efferent fibers. The substantia nigra, pars reticulata, was normal. The type of athetoid motor disability which the patient exhibited may be assigned to this insufficiency of the pallidum.

It may be assumed that the circuit through the pallidum is of a topical nature which regulates the flow of impulses into various groups of muscles, to give compound associated movement. Normal muscular movement requires selective and well balanced reciprocal innervation of the opposing muscle groups. This synergic function may be assigned properly to the corpus striatum. This structure may be thought of as a differential mechanism for guiding the flow of the corticocerebellar impulses into the lower motor apparatus in a reciprocal manner.

How the reciprocal flow is regulated is not clear. The dual nature of the efferent pallidal and striatal connections suggests a double, if not reciprocal, function in the corpus striatum.[21] It is evident that the extrapyramidal flow from the cerebral cortex is through the lateral lobe of the cerebellum, the brachium conjunctivum, the thalamus, the corpus striatum, the red nucleus and the rubrospinal and other extrapyramidal tracts, bilaterally. The double nature of afferent connections to the cerebellum, one through the brachium pontis and the other through the inferior olive, suggests that the flow through the cerebellum is also double and subject to reciprocal modulation in the cerebellar cortex.

In this case the extrapyramidal pathways from the cortex through the cerebellum were open to function through the red nucleus and the striatum. The pallidal pathways alone were largely closed to function.

It is probable that the inhibition or relaxation which the patient could exercise was cortical, influencing either both the pyramidal and the extrapyramidal system or the pyramidal system alone.

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21. Hunt, J. R.: The Existence of Two Distinct Physiological Systems for the Transmission of Motor Impulses in the Peripheral Nerves, Brain **41**:302-331, 1918. Walshe, F. M. R.: On the Genesis and Physiological Significance of Spasticity and Other Disorders of Motor Innervation, with a Consideration of the Functional Relationships of the Pyramidal System, ibid. **42**:1-28, 1919. Wilson, S. A. K.: Disorders of Motility and of Muscle Tone with Special Reference to the Corpus Striatum, Lancet **2**:1-10, 53-62, 169-178, 215-219 and 268-276, 1925. Winkelman, N. W.: Progressive Pallidal Degeneration: A New Clinicopathological Syndrome, Arch. Neurol. & Psychiat. **27**:1-21 (Jan.) 1932. Davison, C.: Anatomy and Physiology of the Extrapyramidal System, in Blumer, G.: Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1936, vol. 9, chap. 29, pp. 791-796. Alcock, N. S.: A Note on the Pathology of Senile Chorea (Non-Hereditary), Brain **59**:376-387, 1936.

The overflow and tonic innervation may be assigned to functional imbalance of the pathways which remained open to function. It is possible that there is a special mechanism for cocontraction. It is suggested that the corticonigric fibers (lateral pontile fasciculi), which were deficient in this patient, may have participated in this phase of the muscular dystonia.

Tonic innervation has been noted in cases of cortical lesions,[22] and removal of the premotor cortex reduces the dystonic athetoid symptoms.[14a] This suggests the cortical initiation of these disturbances. It illustrates the nature of cortical dominance over the subcortical motor apparatus in man.

In cases of severe involvement, training in relaxation is not effective. Surgical section of the extrapyramidal tracts in the cord has been tried by Putnam.[23]

The cause of the pallidal lesions in this case remains obscure. It obviously dates to birth. The history of precipitate labor, the meningeal scars at the base of the skull, the absence of lenticulostriate arteries bilaterally, the general agenesis of the pallidal segments and the reduction of the insular regions suggest an injury at birth. Basal hemorrhages in this region are often seen in still born infants.[24]

SUMMARY

A case of juvenile dystonic athetoid paralysis associated with bilateral agenesis of the globus pallidus and its efferent tracts is described. The contribution of the pallidum to the extrapyramidal motor functions is discussed. The cause of the lesion appears to have been a vascular injury at the base of the brain.

22. Wilson, S. A. K., and Walshe, F. M. R.: The Phenomenon of "Tonic Innervation" and Its Relation to Motor Apraxia, Brain **37**:199-246, 1914.

23. Putnam, T. J.: Treatment of Athetosis and Dystonia by Section of Extrapyramidal Motor Tracts, Arch. Neurol. & Psychiat. **29**:504-521 (March) 1933.

24. Phelps, W. M.: Cerebral Birth Injuries: Their Orthopedic Classification and Subsequent Treatment, J. Bone & Joint Surg. **14**:773-782, 1932. Doll, E. A.: Birth Lesion as a Category of Mental Deficiency, Am. J. Orthopsychiat. **3**:1-13, 1933. Brockway, A.: The Problem of the Spastic Child, J. A. M. A. **106**:1635-1638 (May 9) 1936.

ETIOLOGIC STUDY OF LANDRY'S ORIGINAL CASE OF ACUTE ASCENDING PARALYSIS

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From the report of a case of acute ascending paralysis by Landry in 1859 to the present, there has existed the greatest confusion concerning the localization of the lesion. Landry stated that autopsy showed evidence of recent pleurisy and pneumonia, with no appreciable lesion of the nervous system. However, he did not examine the peripheral nerves and it is generally agreed today that the syndrome was that of acute progressive polyneuritis. That an infectious process was the cause seems to be taken for granted. Landry reported the case history as follows:[1]

Acute generalized ascending paralysis. Autopsy. No appreciable lesion of the nervous system.

Jean Baptiste Grellier, aged 43, a road paver, entered the Hôpital Beaujon on June 1, 1859. He was small in stature, of frail constitution, emaciated and of poor color. He was not of a seclusive disposition.

The patient's father died at the age of 68, having been paralyzed for the last years of his life. His mother, brothers and sisters had never had any illness similar to that which brought the patient to the hospital.

The patient was sickly during childhood. He was said to have had a resistant intermittent fever from the age of 4 to that of 9 years, after which he did not regain strength. He had articular rheumatism of long duration at the age of 15. From this time until 1858 his health was good except for a few slight illnesses from time to time, which he could not describe. He admitted having had gonorrhea followed by swelling and pain of the testes, but there was no chancre or engorgement of the inguinal glands.

From 1858 to 1859 Grellier's health was disturbed by a series of almost continuous illnesses, of more or less severity. In July 1858 he was suddenly taken with a chill, followed by fever and general malaise and then by vague symptoms which he could not describe. He remained several weeks in bed; no active treatment was instituted. Convalescence was brief and complete. Appetite and strength returned promptly.

Three months later, in November, he suffered another chill accompanied by fever and pain in the left arm, which later spread to all four extremities. The patient could not say whether the pain had been more intense in the region of the joints or in the soft parts, but he maintained that there had been no redness or swelling. Pain was continuous, severe and more or less acute on motion. It lasted three weeks, during which time he remained in bed intermittently. He improved

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From the Neurological Unit, the Boston City Hospital.

1. Landry, O.: Note sur la paralysie ascendante aiguë, Gaz. hebd. de méd. **6**:472 (Jan.) 1859.

and returned to his work as road builder until March 16. However, appetite was poor and often absent; strength did not return; he became fatigued easily, and there was vague general malaise.

At the beginning of January 1859 indefinite symptoms related to the posterior part of the pharynx manifested themselves. Difficulty in swallowing and slight, incessant cough were provoked by the sensation of a foreign body in the pharynx. Finally, there was more or less pain, but no fever. These symptoms persisted with alternate remissions and exacerbations, without ever becoming very painful.

On March 16 Grellier, while at work, suddenly experienced a chill with a stitch in the side and cough. Fever followed immediately, and he raised large amounts of sputum. The physician who was called said that the patient had "inflammation of the lungs" and bled him three times. He then administered emetics, blistered him several times over the left posterior portion of the thorax and prescribed a severe diet. For eighteen days the patient took no nourishment. At the end of this time he was permitted some bouillon. Convalescence was slow; the patient could not return to work until May 9; at this time he was still very weak and ate little. His strength, far from returning, persistently diminished. On May 15 he gave up work and, feeling the weakness increasing, returned to the hospital on June 1.

From May 11 or 12 the patient had experienced formication of the ends of the fingers and toes. These sensations, except for the slight discomfort, remained limited to the parts indicated, and Grellier had not paid much attention to them. Aside from generalized weakness, he remained in command of all his movements, and, except for the unaccustomed fatigue which bothered him, all the muscles rendered their habitual service. On June 1 he came without difficulty from Boulogne-sur-Seine to the Hôpital Beaujon on foot and until June 13 presented no appreciable symptoms. He complained only of generalized weakness. From his appearance his complaints seemed exaggerated, and M. Gubler, finding no reason to believe him, doubted his sincerity.

On June 13 Grellier noticed that while walking his knees often gave way under him. The next day this weakness became more pronounced; his feet seemed chained to the ground. For several days the paresthesia had involved the feet and gradually the legs, thighs and arms. These sensations advanced upward, forming a tight band around the affected parts. On the following day the patient walked with great difficulty, dragging his legs. On June 17 he could neither walk nor stand alone.

The weakness spread to the trunk, the muscles of respiration, the neck and the tongue. Loss of motility was more pronounced in the distal portion of the extremities. The sphincters were never affected. Fever was not present, and the pulse rate was from 85 to 90 per minute. The reflexes were lost. There were no fibrillations, and all the muscle groups responded to faradic stimulation. There was no pain, and the patient's mind remained clear. The movements of the eyes and face remained normal. A feeling of constriction about the thorax and some loss of sensation in the feet developed. He complained of paresthesia and stiffness of the cheeks, and the voice became feeble at times. Dyspnea and cyanosis became more marked; while being lifted to a sitting position he became pale and died suddenly, eight days after the onset of the first symptoms of weakness.

Several features of this beautiful case history assist in the diagnosis: The five week interval between the onset of the paresthesia and the weakness, the absence of facial paralysis, the presence of paresthesia

over the cheeks and the weakness of the voice. The apparent cardiac death and the history, almost unbelievable today, of a dietary insufficiency of six months' duration, culminating in bleedings, administration of emetics and eighteen days of starvation during a severe infection, point toward an etiologic factor in the polyneuritis. Who, in this vitamin-conscious age, will deny that Jean Baptiste Grellier died of beriberi?

412 Beacon Street.

Technical and Occasional Notes

HERNIATION OF THE BRAIN NOT HERETOFORE DESCRIBED

ISIDORE FINKELMAN, M.D., CHICAGO

As a distant effect of tumor of the brain and other intracranial disorders, there may be herniations of the brain into all possible openings into which cerebral tissue may be molded, as illustrated in the well known cases of bulging of the third ventricle, a pressure cone at the foramen magnum and minor cortical protrusions at the location of the arachnoid villi. Herniations which have received less emphasis in the literature are those of the fornicate gyrus under the free edge of the falx cerebri and of the uncus and subiculum of the cornu ammonis under the free edge of the tentorium. These were described by Meyer [1] in 1920. Without reference to the work of Meyer, Vincent and his co-workers [2] described herniation of the uncus as a temporal pressure cone. In this article, the authors said that they first described the lesion in 1930 before the Société de Neurologie de Paris.

MATERIAL STUDIED

Seventy-seven brains from the pathologic material of Dr. Loyal Davis were studied. In 61 cases a tumor was present. In 16 cases there was an abscess of the brain, hydrocephalus, subdural hematoma, meningitis or aneurysm.

All types of herniation described in the literature were observed in this material and were analyzed. The present note is concerned with a hitherto undescribed form of herniation, which occurred in 42 per cent of the cases. In this type the base of the frontal lobe bulged backward and downward over the edge of the sphenoid ridge, compressing the tip of the temporal lobe (fig. 1 *A* and *B*). In 80 per cent of the cases of tumor of the frontal lobe this herniation occurred. Herniation over the sphenoid ridge was at times bilateral, the larger protrusion frequently occurring in the hemisphere opposite the site of the tumor. In 50 per cent of the cases herniation over the sphenoid ridge was associated with hydrocephalus, and in 58 per cent, with choked disk. The same correlation with hydrocephalus and papilledema occurred in the material as a whole, in which herniations of all types were grouped together.

At a meeting of the Central Neuropsychiatric Association in Chicago on Oct. 9, 1937, I reported on another type of herniation of the brain as yet undescribed,

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From the Department of Nervous and Mental Diseases and the Division of Surgery, the Northwestern University Medical School.

1. Meyer, A.: Herniation of the Brain, Arch. Neurol. & Psychiat. **4**:387 (Oct.) 1920.

2. Vincent, C.; David, M., and Thiébaut, F.: Le cône de pression temporal dans les tumeurs des hémisphères cérébraux, Rev. neurol. **65**:536, 1936.

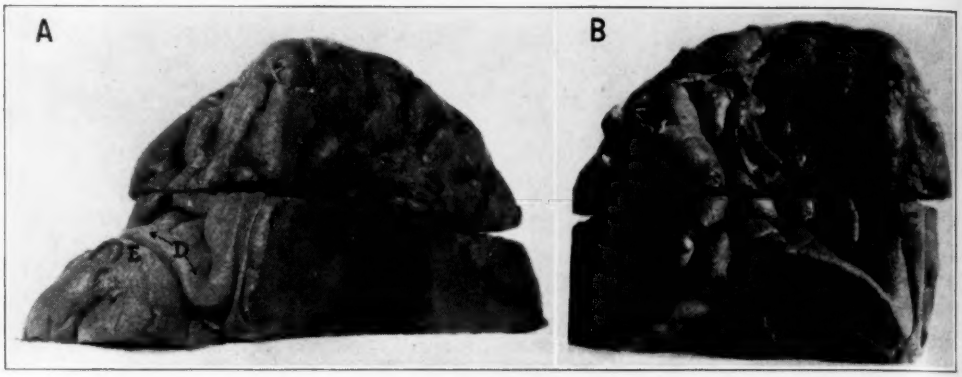

Fig. 1.—*A*, herniation of the right frontal lobe (*D*), with compression of the tip of the temporal lobe (*E*) in a case of glioblastoma multiforme in the left frontal lobe. *B* shows the same brain as that illustrated in 1 *A*, with the temporal lobe removed. *C* indicates the olfactory tract.

Fig. 2.—Herniation of the gyrus rectus (*B*) in a case of glioblastoma multiforme in the right frontal lobe. *A* indicates the optic chiasm.

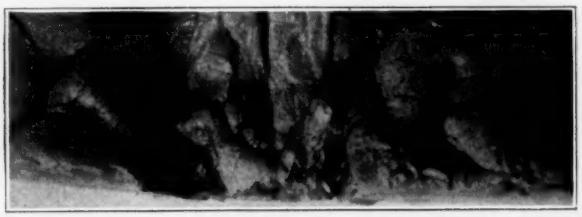

Fig. 3.—Herniation of the gyrus rectus (*B*) in a case of glioblastoma multiforme of the right temporo-occipital region. *A* indicates the anterior angle of the chiasm into which the gyrus rectus herniated.

that of the gyrus rectus.[3] The posterior part of the gyrus rectus was herniated downward and backward over the edge of the limbus sphenoidalis, compressing the optic nerve (figs. 2 and 3). Whereas in other forms of herniation of the brain there was no correlation with secondary hydrocephalus or choked disk, in 9 of the 10 cases of herniation of the gyrus rectus choked disk was observed. In 60 per cent of cases of this herniation there was associated hydrocephalus.

3. After the presentation of this paper, a description of this herniation by T. Hasenjäger and H. Spatz appeared (Ueber örtliche Veränderungen der Konfiguration des Gehirns beim Hirndruck [Zisternenverquellung and Verschiebung über die Medianebene], Arch. f. Psychiat. **107**:193, 1937).

SPECIAL ARTICLES

THE CENTENARY OF MULTIPLE SCLEROSIS

TRACY J. PUTNAM, M.D.
BOSTON

The first pathologic specimen in a case of multiple sclerosis was described and illustrated by Sir Robert Carswell, professor of pathologic anatomy at the University College, London, in an atlas published serially up to 1838.[1] According to Bourneville and Guérard,[2] the illustrations for the atlas were drawn in Paris, but this is not apparent from the book itself. They are signed by Carswell himself as artist; some are annotated as being drawn directly on the lithographic stone. The earlier plates, among them the one on multiple sclerosis, are marked as being printed by "lithographers to the King," and the later ones, by "lithographers to the Queen"—that is, presumably subsequent to June 1837. It is likely, therefore, that the fascicle containing the description of multiple sclerosis was prepared in England and published in 1836 or 1837. Carswell's illustration (fig. 1) is unmistakable, and his description is concise.

Fig. 4, a peculiar diseased state of the chord and pons Varolii, accompanied with atrophy of the discoloured portions; A., right crus; B, left crus cerebri; C, pons Varolii; D, medulla oblongata; E, E, Medulla spinalis; F. F. isolated points of the pons Varolii, of a yellowish brown colour; G, G, G, patches of the same kind on the spinal chord, all of them occupying the medullary substance, which was very hard, semitransparent, and atrophied. The atrophy was more conspicuous in some points than in others, and is particularly well seen in the figure at H, where it affects a portion of the right olivary body; K, softening of a portion of the chord. Figure 4, A and B, represents transverse sections of the chord, to show that the discolouration commences on the surface of the white, and extends inwards to the gray substance; A, the brown discolouration which has extended to the grey substance on one side of the chord, a; and is confined to the white substance on the other side, b. Similar appearances are represented in the section B, a, b.

From the Neurological Unit, the Boston City Hospital, and the Department of Neurology, Harvard University Medical School.

The expenses of preparation of this paper were defrayed by a grant from the John and Mary R. Markle Foundation to the Multiple Sclerosis Fund of Harvard University.

1. Carswell, R.: Pathological Anatomy: Illustrations of the Elementary Forms of Disease, London, Longman [and others], 1838.

2. Bourneville and Guérard, L.: De la sclérose en plaques disséminées, Paris, A. Delahaye, 1869.

It is of interest to note that there was a fresh softening of the cord, as well as the old scars—evidence of the relationship between acute myelitides and chronic disseminated sclerosis, which has often been reported since, and as often forgotten. Carswell suggested that all primary atrophy of the central nervous system is due to a deficiency of blood supply.

The credit for the first description of multiple sclerosis is usually given to Cruveilhier,[3] doubtless owing to the plausible and widely read

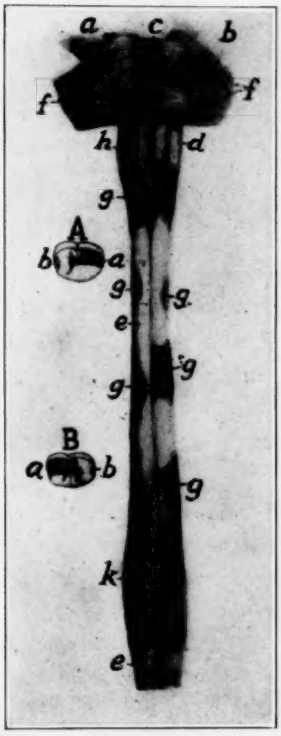

Fig. 1.—"A peculiar diseased state of the chord and pons Varolii" (after a lithograph by Carswell[1]).

historical note contained in Charcot's[4] lectures and the book written by Charcot's pupil Bourneville.[2] The description of the disease given by Cruveilhier was published in the second volume of his magnificent "Atlas," which began to appear in serial form in 1835. Charcot intimated that this should be taken as the date of the description of multiple

3. Cruveilhier, J.: Anatomie pathologique du corps humain, ou descriptions avec figures lithographiées et coloriées, des diverses altérations morbides dont le corps humain est susceptible, Paris, J. B. Baillière, 1835-1842, vol. 2.

4. Charcot, J. M.: Histologie de la sclérose en plaques, Gaz. d. hop. **41**:554-555, 557-558 and 566, 1868.

sclerosis. Examination of the thirty-second *livraison,* in which the first report stands, reveals, however, that some of the patients autopsies on whom were illustrated did not die until 1838. Charcot spoke of being engaged in writing one of the histories on Nov. 30, 1838—unquestionably, after Carswell's publication. The volume was completed in 1842.

Cruveilhier's fame needs no artificial support, however, for he was the first to record the history with pathologic correlation in a case of multiple sclerosis (fig. 2). The report is so important as to deserve abstraction.

Paraplegia; degeneration of the gray matter of the spinal cord, bulb, protuberance, cerebellar peduncles, optic thalami, corpus callosum and fornix.

Darges, a cook aged 37, . . . had been ill six years without known cause. Six years ago she noticed that the left leg resisted her will to such a degree that she fell in the street. Three months later the right leg was affected like the left. The upper extremities finally became . . . tremulous and weak. Sensation was unaffected . . . I noticed no spasmodic retraction and no painful spasms of the extremities. . . . She gave a complete history, although the articulation of sounds was embarrassed. . . . When I spoke to her she became seized with an emotion difficult to describe. She blushed, laughed and cried; the extremities and trunk became the seat of involuntary movements. . . . Swallowing was difficult. . . . There was never any headache. She complained of feebleness of vision.

I had made the diagnosis of a lesion of the upper portion of the spinal cord. I was even tempted . . . to consider the disease due to compression of the medulla . . . by a tumor, . . . but the complete absence of headache caused me to abandon this idea.

A second case report, also accompanied by an excellent illustration, was published in the thirty-eighth *livraison* of the same "Atlas." In Cruveilhier's opinion, the disease was due to suppression of sweat, as was rheumatism.

There appear to be no recognizable records of cases prior to the almost simultaneous reports of Carswell and Cruveilhier. In Romberg's textbook on nervous diseases (1846),[5] there is recorded a questionable case of a young woman who had hemiplegia, first on one side and then on the other, and was observed at autopsy to have "yellow softenings" about both lateral ventricles. The learned author cited no parallel instances, however. According to Charcot,[4] the disease was often confused with paralysis agitans, but surely none of Parkinson's [6] patients suffered from it. A survey of the great collections of Bonet [7]

5. Romberg, M. H.: Lehrbuch der Nervenkrankheiten des Menschen, Berlin, A. Duncker, 1846.

6. Parkinson, J.: Essay on the Shaking Palsy, London, Sherwood, Neely and Jones, 1817. Ostheimer, A. J.: An Essay on the Shaking Palsy, by James Parkinson, M.D., Member of the Royal College of Surgeons, with a Bibliographic Note Thereon, Arch. Neurol. & Psychiat. **7**:681-710 (June) 1922.

7. Bonet, T.: Sepulchretum, sive anatomia practica ex cadaveribus morbo denatis, Geneva, L. Chouët, 1679.

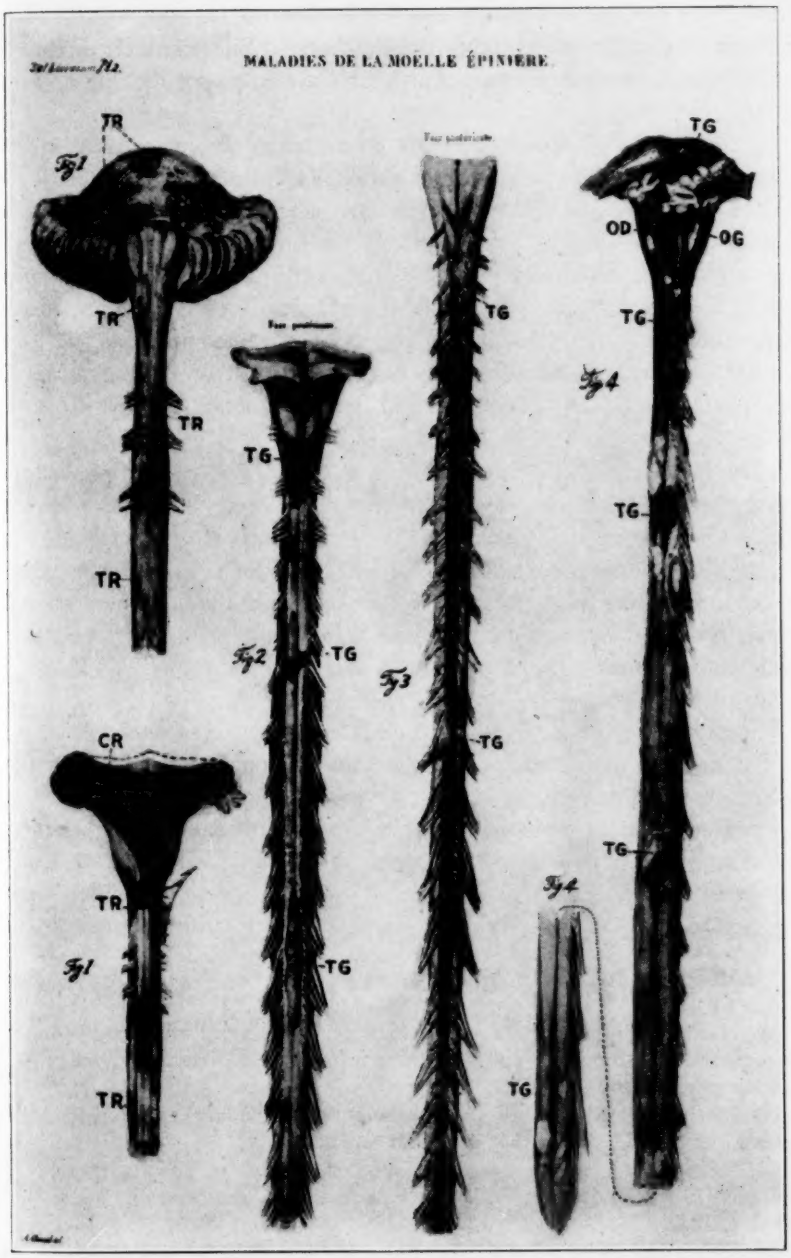

Fig. 2.—"Maladies de la moëlle épinière" (after a lithograph in Cruveilhier's "Atlas," [3] 1839?).

and Morgagni [8] reveals nothing suggestive of multiple sclerosis, nor do the scholarly and well documented treatises of Haslam,[9] Pinel [10] and Calmeil [11] contain any recognizable cases. The clinical picture of "paralysis of the insane" formulated by Calmeil might include a case of multiple sclerosis.

A diagnosis of spinal sclerosis in a living patient was apparently first made by Frerichs, and his pupil Valentiner [12] is credited with establishing a clinical picture. Valentiner's article includes in one group cases of tabes dorsalis, combined sclerosis and multiple sclerosis; of the last-named disease, the author adds only 2 new cases to Cruveilhier's 2. Except for paraplegia, the clinical description is obscure. Valentiner, however, pointed out the existence of remissions.

A case occurring in this country, in which a histologic examination was performed by S. Weir Mitchell, was well described by Morris, in 1868.[13]

The main contributions of Charcot to the subject of mutiple sclerosis were three. First, he laid down certain clear, though somewhat arbitary, criteria of diagnosis.[14] According to Bourneville and Guérard,[2] Charcot became familiar with the progress of the disease through watching its gradual development in a maid employed in his house, who had nystagmus, intention tremor and scanning speech. He made the diagnosis of tabes dorsalis, but autopsy showed disseminated areas of sclerosis.

Second, Charcot gave the first clear and complete histologic account of the lesions. By means of free hand sections or teased specimens, examined fresh or stained with carmine, he made out the loss of myelin, the preservation of axis-cylinders, the proliferation of glia fibers and nuclei and the perivascular accumulation of fat-laden phagocytic cells. He drew with his own hands (fig. 3) the illustrations, which served the textbooks of a generation. Further, he described certain details

8. Morgagni, J. B.: De sedibus et causis morborum, Venice, Remondineana, 1761.

9. Haslam, J.: Observations on Insanity, with Practical Remarks on the Disease, and an Account of the Morbid Appearances on Dissection, London, F. & C. Rivington, 1798.

10. Pinel, L.: Recherches d'anatomie pathologique sur l'endurcissement au systéme nerveux, J. de physiol. expér. **2**:191-200, 1822.

11. Calmeil, L.: De la paralysie considérée chez les aliénés, Paris, J. B. Baillière, 1826; Traité des maladies inflammatoires du cerveau, Paris, J. B. Baillière, 1859.

12. Valentiner, W.: Ueber die Sklerose des Gehirns und Rückenmarks, Deutsche Klin. **8**:147, 158 and 167, 1856.

13. Morris, J. C.: Case of the Late Dr. C. W. Pennock, Am. J. M. Sc. **56**: 138, 1868.

14. Charcot, J. M.: Diagnostique des formes frustes de la sclérose en plaques, Progrès méd. **22**:97-99, 1879.

which are often neglected today: the fact that in many plaques the axis-cylinders are greatly diminished in number and that the walls of the smaller vessels are often thickened and their lumens obstructed.[4] The modern development of new and specific staining methods has

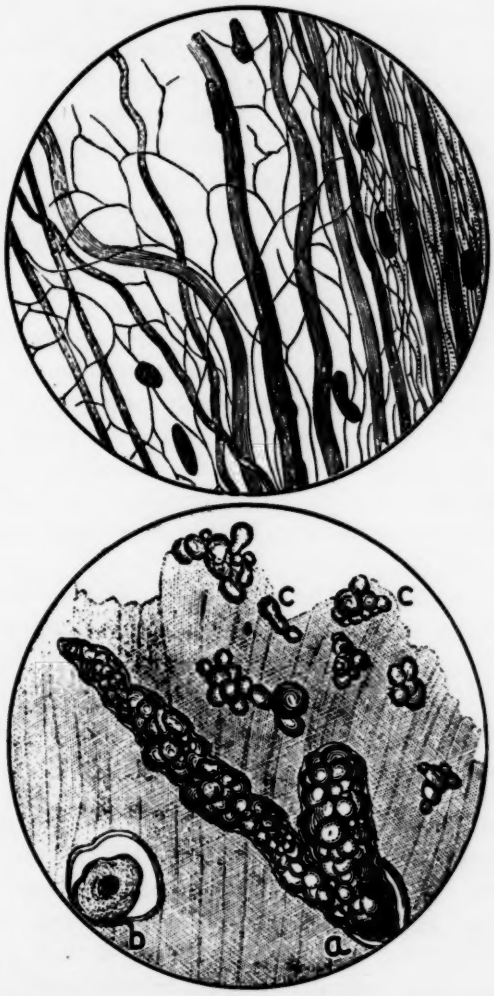

Fig. 3.—Histologic structure of a lesion of multiple sclerosis (after a woodcut by Charcot,[4] 1868). On the left a capillary surrounded by naked axis-cylinders and gliosis is seen in a teased specimen. On the right perivascular infiltration with fat-laden cells is illustrated.

added almost nothing to his description; indeed, it has to some extent tended to distort it, since the stains of the Weigert type have drawn

attention to the dramatic changes in the myelin and away from the perhaps more significant alterations in other tissues. Charcot expressed the belief that the hypertrophy of glia fibers is the primary pathologic alteration—a conception which still leaves its mark.

Nearly thirty years after the publication of his first paper on the subject, Charcot returned to it to point out that many cases exist in which the "triad" of symptoms is not found and that the diagnosis could and should be made in the early, mild *formes frustes*.[14] In modern practice the atypical forms appear to be more common than the "classic" ones, and the diagnosis is accordingly made with increasing frequency.

Of the sufferers from multiple sclerosis, perhaps the most famous was Heinrich Heine.[15] It is usually stated that he died of tabes dorsalis, which was the diagnosis made at the time of his death, but at that period the clinical recognition of multiple sclerosis had scarcely been attempted. His illness began with transient palsy of both hands (1832). Five years later sudden bilateral amblyopia occurred with dilatation of the left pupil. It gradually improved, then progressed toward the end of his life. In 1843 there were ptosis of the left lid and hyperesthesia of the left side of the face. Symptoms of bulbar involvement appeared in 1846, but disappeared in 1850. About 1846 ataxic paraplegia also began and progressed to the time of his death, in 1856.

A harrowing account of the experiences of a brilliant young man gradually becoming incapacitated by multiple sclerosis is given by Barbellion.[16]

Multiple sclerosis was considered something of a curiosity even by Charcot. Most of the articles written about it in the last century dealt with 1 case, or with a small number at most. With the decline of the incidence of neurosyphilis and the progress of refinements in diagnosis it is rapidly coming to be known in many parts of the world as the commonest disease of the nervous system after epilepsy and the senile cerebral diseases. Von Hoesslin[17] collected the records of 516 cases from the hospitals of Munich. The Multiple Sclerosis Commission of the American Neurological Association is reviewing the histories of over 500 cases. A comparison with other well known diseases is of interest: At the Boston City Hospital, in the five years from 1931 to 1935, the diagnosis of subacute bacterial endocarditis was verified in

15. Schachter, M.: Un illustre malade: Le poète Henri Heine, Paris méd. (supp.) **1**:vi-viii, 1933.

16. Barbellion, W. N. P.: The Journal of a Disappointed Man, New York, George H. Doran Co., 1919.

17. von Hoesslin, R.: Ueber multiple Sklerose: Exogene Aetiologie, Pathogenese, und Verlauf, Munich, J. F. Lehmanns Verlag, 1934.

50 cases; the diagnosis of poliomyelitis was made in 101 new cases, and the diagnosis of multiple sclerosis was made in 203 cases. Yet the natural history of poliomyelitis is familiar even to the laity, and enormous sums are expended on its study, while even among medical men multiple sclerosis is often referred to as a "rare and mysterious" diease, which deserves no more than a passing interest.

The story of knowledge of multiple sclerosis is like a history of medicine in miniature. The disease as an entity was lost in empiric descriptions of individual symptoms, up to the time when definite pathologic change was recognized. The range of clinical syndromes could then be gradually explored and described, since they had a fixed point of reference in the anatomic picture. Many histologists have described and redescribed the pathologic process with such minuteness that it seems unlikely that anything substantial is to be learned about the steps of parenchymal breakdown and repair. Empiric forms of treatment have encouraged the optimistic, but a rational therapy can scarcely be expected before the pathogenesis of the disease is understood. The story of multiple sclerosis is not yet closed, but neither is the history of medicine.

Obituary

WILLIAM K. WALKER, M.D.
1867-1938

Dr. Walker was born in Phoenixville, Pa., in 1867 and was graduated from the University of Pennsylvania School of Medicine in 1891. After serving for more than a year at the University Hospital and the Philadelphia Orthopaedic Hospital, he studied in Paris. On his return from Europe he became associated with Dr. Charles A. Oliver, of Philadelphia, and afterward with Dr. H. V. Würdeman, of Milwaukee, in the practice of ophthalmology for one or two years. After this, he became assistant superintendent of the Dixmont Hospital for the Insane, at Dixmont, Pa., near Pittsburgh, where he worked for twelve years. He then entered private practice in psychiatry and neurology in Pittsburgh. At the same time he became professor of psychiatry in the University of Pittsburgh School of Medicine and attending physician to the psychopathic department of St. Francis Hospital. He was also neuropsychiatrist to the Western Pennsylvania Hospital during his years of private practice in Pittsburgh. He retired from active practice in 1927 and spent the remainder of his life at his old home in Phoenixville, Pa., in semi-retirement.

Dr. Walker was an earnest student and a persistent investigator. He was the author of many papers produced as a result of careful investigation. He not only was well read in medical literature but was a man of wide culture. He was earnest, diffident and retiring; life was more difficult for him than for most men. He was greatly appreciative of the amenities and courtesies of life—always dignified and considerate of the rights of others. His sense of humor was keen, and he knew a good story and frequently told some of the best. He was meticulous in manner, conduct and dress. His personality was definitely expressed and appreciated by a wide circle of colleagues, friends and patients.

Dr. Walker's medical society affiliations included membership in the Allegheny County and Pennsylvania State Medical societies, the Pittsburgh Academy of Medicine, the American Medical Association, the Pittsburgh Neurological Society and the American Neurological, the American Psychopathological and the American and the International Psychoanalytical Association. He was a member of the University Club of Pittsburgh and the Pennsylvania and the Valley Forge Historical Society.

THEODORE DILLER, M.D.

Abstracts from Current Literature

Anatomy and Embryology

THE ROLE OF JACOBSON'S ORGAN IN THE FEEDING REACTION OF THE COMMON GARTER SNAKE, THAMNOPHIS SIRTALIS SIRTALIS (LINN.). WALTER S. WILDE, J. Exper. Zoöl. **77**:445 (Jan.) 1938.

The organs of Jacobson, a part of the olfactory apparatus in air-breathing vertebrates, are a pair of blind sacs opening on the median nasal walls or the anterior palate or in the nasopalatine ducts. Their lining contains typical olfactory cells, the axons of which form the vomeronasal nerve, a branch of the olfactory nerve, which is distributed to the accessory olfactory bulb. The common garter snake strikes blindly with open mouth when either the tongue or the lips make contact with anything (e. g., a cotton swab) wet in a solution of the slimy mucus from earthworms. This response is to chemical stimulation, since visual or tactile stimuli afforded by swabs wet in water do not elicit it, whereas scalded earthworms, or even cotton swabs wet in the mucus of earthworms, are ingested. The strike response is evoked through the organ of Jacobson by way of its olfactory cells and vomeronasal nerve, since surgical elimination of either the organ or the nerve abolishes the response but cutting the bulk of the olfactory nerve does not. The flickering tongue plays a part in the transport of stimulating material to Jacobson's organs, but it is necessary only for the tongue to leave the material on the palate. The mechanism of transport of stimulating substances from the palate to the organs is unknown.

WYMAN, Boston.

AN ANALYSIS OF CELLULAR PROLIFERATION IN GRAFTED SEGMENTS OF EMBRYONIC SPINAL CORD. LEONA RUTH ZACHARIAS, J. Exper. Zoöl. **78**:135 (April) 1938.

Three or four segments (6, 7, 8 and 9) of the spinal cord, with the adjacent myotomes and notochord, were transplanted heterotopically into the corresponding somitic region of host embryos of Amblystoma punctatum. Grafts were transplanted from donors in Harrison's stage 22 to hosts in stages 22, 27 and 32 and from donors in stages 27 and 32 to hosts of the same ages. The segmentation of the transplanted cord, the formation of the spinal ganglia and the outgrowth of the spinal nerves were normal except that the length of segments of the grafted cord was about 70 per cent that of segments of the normal cord. Transverse sections of grafted cord contained about 30 per cent more cells than corresponding sections of cord of the host. The cellular content of the grafted segments, however, was about the same as, or slightly less than, that of the corresponding segments of the host. Zacharias concludes that the cells of the isolated segments tend to proliferate to the normal definitive number characteristic for these segments and that the hyperplasia reported by other authors was only apparent, because of the shortening and thickening of the transplanted segments. The results of counts of mitotic figures substantiated the conclusion derived from the cell counts.

WYMAN, Boston.

EPENDYMAL STREAKS AND ACCESSORY CAVITIES IN THE HUMAN OCCIPITAL LOBE. A. F. LIBER, J. Neurol. & Psychiat. **1**:17 (Jan.) 1938.

The frequent variability in form of the occipital horn of the lateral ventricles led Liber to investigate this condition as a routine. In sixteen of fifty unselected human brains he observed small accessory occipital cavities caudad to the tip of the posterior horn, more frequently in the right hemisphere. These cavities were all lined with ependyma. In addition, Liber observed in this location, in the

majority of brains, ependymal streaks made up of a solid single or double row of ependymal cells flanked by subependymal tissue, frequently containing microscopic cavities and rosettes. The few cases in which neither of these anomalies was present occurred as a rule in the brains of infants. In these brains the occipital horn was round, whereas in the majority of adult brains it was flat. It appears, then, that in the embryo a primary broad, round occipital horn exists. In the course of extra-uterine development the posterior horn becomes obliterated by the growth of the surrounding structures, namely, the calcar avis, the callosal bulb, the tapetum, the collateral eminence and the optic radiations. This process of obliteration explains the origin of the ependymal streaks, the accessory cavities and the variability in form of the occipital horn.

N. MALAMUD, Ann Arbor, Mich.

ANALYSIS OF FIBERS OF THE PYRAMIDAL TRACT. G. HAGGQUIST, Acta psychiat. et neurol. **12**:457, 1937.

It has been pointed out by many anatomists that not all the fibers contained within the lateral corticospinal tract in the spinal cord belong to the corticospinal system. The fibers contained in this area vary in diameter from 1 to 21 microns. This difference in diameter points to a difference in the speed of conduction of impulses and makes it improbable that all the fibers belong to the same functional system. In order to elucidate this problem, Häggquist made a comparative count of fibers in cross sections of the pyramids of the medulla oblongata in 4 rhesus monkeys killed two months after extirpation of various regions of the right frontal lobe. In a rhesus monkey with extirpation of the upper portion of the right area gigantopyramidalis, resulting in hemiparesis of the left arm and leg, the count showed a considerable reduction in the number of fibers between 3 and 4 microns in diameter in the right pyramid; fibers over 10 microns were all degenerated. In a rhesus monkey with extirpation of the lower portion of the right area agranularis, resulting in monoparesis of the left arm without marked involvement of the leg, the count showed a reduction of the fibers between 3 and 8 microns in diameter in the right pyramid; the fibers less than 3 and more than 8 microns in diameter were present in equal numbers in both pyramids. In a rhesus monkey with extirpation of the uppermost portion of the right frontal lobe, resulting in paresis of the left arm and leg, the fiber count in the right pyramid showed a marked reduction of fibers over 3 microns and total degeneration of fibers over 11 microns in diameter. In the fourth rhesus monkey the lower portion of the right frontal lobe was removed, with resulting flexion contracture of the left arm and leg; the fiber count in the right pyramid showed some reduction of fibers between 2 and 3 microns in diameter; most of the fibers from 3 to 6 microns in diameter were lost; the number of fibers between 6 and 7 microns in this pyramid was not much reduced as compared with that in the left pyramid, but the number of fibers over 7 microns was much reduced and the fibers of 11 microns were all degenerated. From these results the author concludes that about five sixths of the fibers contained in the pyramid of the medulla are not corticospinal, but belong to other systems. The fibers of the corticospinal system proper are 3 microns or more in thickness. These fibers are distributed evenly throughout the cross section of the pyramid. There is no evidence of any special increase in their number at the cervical and lumbar levels of the cord. More pyramidal fibers come from the uppermost than from the lowermost portion of the precentral sulcus. From the upper portion of the sulcus originate mostly thick fibers (over 8 microns), whereas from the lower portion thin fibers (from 3 to 8 microns) arise. Since the thick fibers have a higher rate of conduction than the thin fibers, it is of interest to note that the pyramidal fibers for the lower extremities are thicker than those for the upper extremities. The rationale of this is evidently the synchronization of cortical innervation of the proximal and the distal segments of the body.

YAKOVLEV, Waltham, Mass.

Physiology and Biochemistry

ROLE OF ANOXIA IN PRODUCTION OF EPILEPTIFORM SEIZURES. THOMAS SIMPSON and M. HERBERT BARKER, Arch. Int. Med. **61**:208 (Feb.) 1938.

Simpson and Barker devised a method by which patients suffering from epilepsy were subjected to anoxia of varying degrees and duration in order to determine what percentage of oxygen tension in the inspired air would induce seizures. A double oxygen chamber was used, and nitrogen was pumped in to reduce the oxygen content of the inspired air. The patient lived in the chamber; during this period he was allowed much freedom of activity. This eliminated the apprehension coincident with rebreathing experiments. Thirteen patients and a series of 6 dogs serving as controls were studied. The oxygen content of the inspired air was lowered to a level which was thought safe for the particular patient, that is, from 7 to 9 per cent. Preliminary gradual induction of anoxia was used to prevent the undesirable results of "mountain sickness." Usually when the level of oxygen in the inspired air reached 14 per cent, the patient was extremely dyspneic. On exertion and at the level of 9 per cent, he invariably became deeply cyanotic and confused. No typical epileptic convulsions were produced, but all patients demonstrated motor phenomena at oxygen levels corresponding to those producing asphyxia. A phenomenon resembling epilepsy was observed in 5 instances; however, in only 1 was it regarded as a definite seizure, and in another it was questionable. Neither the symptoms nor the acid-base balance of the patients during anoxia differed from those observed in dogs and normal human beings under similar conditions. The authors conclude that anoxia is not the salient factor in the production of epileptic seizures.

BECK, Buffalo.

FAT IN THE INFANT BRAIN IN RELATION TO MYELIN, BLOOD VESSELS AND GLIA. C. R. TUTHILL, Arch. Path. **25**:336 (March) 1938.

Tuthill studied the brains of 46 infants varying in age from birth to 2 years. Fat was observed around the blood vessels and glia cells of the centrum ovale, corpus callosum and white substance of the lower part of the gyri in all of 21 infants less than 4 months of age. Tuthill believes that the fat decreases with the formation of myelin and ceases at the age of 4 months, when myelination in the white substance of the hemisphere is apparently complete. He states that this fat is a waste product of myelin metabolism and occurs in areas of poor capillary circulation, while it is meager or absent in regions of good capillary circulation, such as the internal capsule, basal ganglia, cerebellum and cortex. Perivascular fat is present in the large subcortical vessels from the first month to the end of 2 years of life, apparently as a metabolic product involving the myelin at the junction of the white and the gray substance. The formation of myelin is influenced somewhat by disease, since it varies not only at birth but during the entire period of its development. The astrocytes are mature at the time of myelin formation in the cortex, between the fourth and the ninth month of life. In the white substance of the cerebellum and in the centrum ovale, the chief cell during myelination is a young astrocyte which has a large, clear nucleus and subnuclear cytoplasm with fine processes and pseudopodia. In the centrum ovale these cells are more than twice as many as the oligodendroglia cells during the first and second months; they are equal in number at the age of 6 months and are less than half as numerous at the age of 2 years, although the oligodendroglia cells are fewer than those in the adult brain. The astrocytes of the centrum ovale apparently assist in transferring the waste fat of myelination to the vessels by way of their pseudopodia.

WINKELMAN, Philadelphia.

VITAMIN A AND TUMOR MITOCHONDRIA. ALFRED GOERNER and M. MARGARET GOERNER, J. Biol. Chem. **123**:57, 1938.

It has been shown that 1, 2, 5, 6-dibenzanthracene, a carcinogenic hydrocarbon, depletes hepatic mitochondria of vitamin A. In the mitochondria of tumor cells,

however, vitamin A was found to be absent even when there was an abundant supply in the liver. The total lipid content of mitochondria in sarcoma was lower than that in carcinoma.

PAGE, Indianapolis.

THE EFFECT OF GROWTH ON THE DISTRIBUTION OF WATER AND ELECTROLYTES IN BRAIN, LIVER AND MUSCLE. HERMAN YANNET and DANIEL C. DARROW, J. Biol. Chem. **123**:295, 1938.

The effect of growth on the chemical composition of brain, liver and muscle was studied in cats of different ages. In the brain, growth is associated with a decrease in the concentration of water, sodium and chloride and an increase in the concentration of fat, phosphorus and nitrogen. These changes are related to the growth of the body as a whole, according to Huxley's "constant differential growth ratio." Anatomically, the changes are brought about chiefly by the deposition of lipid in the myelin sheaths, with an associated decrease in the proportion of extracellular fluid. In muscle, growth is associated with a decrease in the concentration of sodium and chloride and an increase in the concentration of nitrogen, phosphorus and potassium. There is little change in the percentage of total water. These changes in chemical composition represent a change in the distribution of water between the intracellular and the extracellular compartments resulting from the growth of the muscle fibers. The relation of the increase in the percentage of intracellular fluid and the decrease in the percentage of extracellular fluid to the growth of the body as a whole also follows the "constant differential growth ratio." The livers of the older animals show an increased concentration of lipids, phosphorus and nitrogen and a decreased concentration of sodium, chloride and water. These changes apparently are all associated with the deposition of lipid and are related to the nutritional status of the animals rather than to growth. Except for a decrease in the concentration of intracellular potassium in the livers of the older animals, no changes are demonstrated in the concentration of nonlipid nitrogen, nonlipid phosphorus or potassium in the intracellular fluid of the tissues studied.

PAGE, Indianapolis.

RESPONSE TO LIGHT IN PERANEMA TRICHOPHORUM WITH SPECIAL REFERENCE TO DARK-ADAPTATION AND LIGHT-ADAPTATION. LANDRUM B. SHETTLES, J. Exper. Zoöl. **77**:215 (Nov.) 1937.

The flagellate protozoan Peranema trichophorum responds to rapid, but not to slow, increase in illumination with rapid deflection of the anterior end. The entire organism is sensitive to light, the sensitivity decreasing from the flagellum to the posterior end. The detached flagellum responds to increase in illumination by bending, especially at the tip, but it does not recover. Stimulation by light is dependent on the wavelength as well as on the intensity. As light adaptation or dark adaptation increases, the reaction time decreases to a minimum in about one-half or one hour, then increases to a maximum in about three hours and remains nearly constant. The greater the intensity to which peranemas are fully adapted, the longer the time in darkness required to neutralize the effect of the light. The reaction time consists of a period of exposure and a latent period. With increase in intensity of illumination the period of exposure decreases until it becomes nearly constant, and the latent period increases to a maximum and then decreases. With increase in temperature the latent period decreases considerably, but the period of exposure decreases only slightly. At least two processes are involved in the response to light, one of which is probably photochemical. Strychnine sulfate causes great increase, and cocaine hydrochloride considerable decrease, in the sensitivity to light.

WYMAN, Boston.

THE REPRESENTATION OF RESPIRATORY MOVEMENTS IN THE CEREBRAL CORTEX. WILBUR K. SMITH, J. Neurophysiol. **1**:55 (Jan.) 1938.

Alterations in breathing, characterized by inhibition or acceleration, were produced by electrical stimulation of certain regions of the cerebral cortex in the cat, dog and monkey (Macaca mulatta). In the cat and dog, when placed under light ether anesthesia, an inhibitory effect on breathing, characterized by temporary cessation or slowing, was most easily elicited from an area in the gyrus compositus anterior. A less marked, but definite, inhibitory effect was obtained from most of the cortex of the sylvian and ectosylvian gyri, and in the cat from the gyrus proreus as well. Increase in the depth of anesthesia resulted in abolition of the response, the area in the anterior composite gyrus being the last to succumb. Stimulation of the inhibitory area not only slowed or arrested panting but abolished or prevented the alterations in breathing that are ordinarily produced by sensory stimulation.

The inhibitory area in the monkey was found to be situated in the cortical field just caudal to the lower end of the sulcus precentralis inferior.

In the cat and dog the acceleratory response was most easily elicited from the rostrolateral part of the anterior sigmoid gyrus and the adjacent cortex forming the caudal wall of the sulcus praesylvius, and in the monkey, from an area just rostral to the sulcus precentralis superior. In the cat and dog the acceleration at times was so great as to simulate panting, but in the monkey an increase in rate of such magnitude was never obtained.

The region from which the acceleratory response was most easily elicited belongs cytoarchitecturally to area 6a in all three animals, and that from which the inhibitory response was most easily obtained, to area 6b.

The presence in the cat, dog and monkey of cortical areas possessing similar cytoarchitectural structure and yielding similar physiologic responses suggests the existence of a fundamental plan for the cortical control of respiration in the general scheme of cerebral cortical evolution.

ALPERS, Philadelphia.

FUNCTIONAL ORGANIZATION IN THE SENSORY CORTEX OF THE MONKEY (MACACA MULATTA). J. G. DUSSER DE BARENNE and W. S. MCCULLOCH, J. Neurophysiol. **1**:69 (Jan.) 1938.

The method of local strychninization combined with recording the electrocorticogram has proved suitable for study of the problem of functional organization within the sensory cortex of the monkey. Local strychninization of the cerebral cortex induces typical changes in the electrocorticogram, namely, the temporary appearance of large, rapid potential fluctuations, or "strychnine spikes." The distribution of these spikes differs with the locus of strychninization. In the visual cortex (area 17 of Brodmann) and in area 5 of the sensory cortex they are restricted to the area strychninized and its immediate vicinity. In the sensory cortex the spikes are widespread, and their distribution is specific for different areas.

The specific differences in distribution described in this paper are the expression of directed relations between the various portions of the sensory cortex, of functional organization within this region.

Local strychninization of two areas of the sensory cortex (areas 4 and 1) results in temporary suppression of the electrocorticogram of areas L 4 and A 4, while "firing" other portions of the sensory cortex.

Experiments with recording the electrocardiogram and local electrical stimulation of various areas of the sensory cortex showed that the distribution of the propagated excitation, manifesting itself in the spread of an electrical after-discharge, was the same as the distribution of the spikes elicited by local strychninization of the same areas.

The observations reported here confirm and amplify the original hypothesis of Dusser de Barenne of an intimate functional interrelation of the various areas within any one major subdivision of the sensory cortex.

ALPERS, Philadelphia.

Psychiatry and Psychopathology

PSYCHIATRIC STUDY OF CAR SICKNESS IN CHILDREN. J. H. CONN, Am. J. Orthopsychiat. **8**:130 (Jan.) 1938.

Conn compared 25 car-sick children (13 girls and 12 boys) between 6 and 12 years of age with a group of 25 patients who were not car sick. The personality of the child and his life situation appeared significant in the occurrence of car sickness. All the 25 car-sick children were described as being emotionally unstable; 17 were timid and submissive in make-up. Among the complaints associated with the car sickness were restlessness, difficulty in falling asleep, nail biting, fear of the dark, enuresis and episodes of vomiting. Nineteen of the patients were found to be poorly nourished. Six children were of superior intelligence; 5 were of limited intelligence, and 14 were of average intelligence. The influence of the life situation was illustrated by a series of play contacts. In several cases the fears of the dark, general apprehensiveness and timidity improved in association with disappearance of the car sickness. One child vomited while riding in a streetcar and in an automobile but was not disturbed while riding in a taxicab. Another patient was car sick only during the winter months. When the child was given a chance to express himself about his experiences on the streetcar and automobile, it was possible to understand such reactions. In the verbatim reports of the play reactions, there was no instance in which a car-sick child stated that the doll was at ease in the toy streetcar. Nor did a child who was not car sick report the anticipation of an accident or speak of the fearfulness of the doll in the toy streetcar.

EDITOR'S ABSTRACT.

CORRELATIONS OF BEHAVIOR AND NEUROPATHOLOGY IN A CASE OF CEREBRAL PALSY FROM BIRTH INJURY. ARNOLD GESELL and HARRY M. ZIMMERMAN, Am. J. Psychiat. **94**:505 (Nov.) 1937.

A boy, who was born at full term after twenty-four hour labor, weighed 10 pounds (4,535 Gm.) at birth. The head was misshapen, though no instruments were used. Stimulation as an aid to respiration was necessary. After nine hours the infant showed twitching of the left cheek. Forty-eight hours after birth he had convulsions, of unknown extent and duration. Deep cyanosis was present; the fontanels bulged and there was marked internal strabismus bilaterally. He had to be artificially fed for ten days. After this time, however, he showed rapid gains, and development was regarded as relatively normal until the age of 6 months, when spasticity, particularly on the right side, was noticed. From that time symptoms of the illness developed rapidly.

The patient came to the notice of the authors at the age of 4 years. From then until his death from appendicitis, at the age of 14, repeated studies were made of the behavior development. When he came under observation, he was slightly in advance of the average child of his age with regard to body length and weight. "He had suffered only a few minor illnesses; slept well, and was not markedly fatiguable. His features and torso were well formed. His countenance was normal, attractive, and expressive for brief intervals when not in the throes of involuntary activity. He could not nod his head, sit up, creep, reach nor manipulate. At times he was quiescent, but under the least excitement, arms, head, fingers, also face, mouth, tongue—and to a lesser degree, legs and toes—went into apparently aimless extensions, flexions and rotations, with antagonistic muscles shifting their ascendancy. Occasionally the double athetosis became extreme, the movements on the right side being most pronounced and abrupt. There was recurrent spacticity. Crossing of the legs disappeared on relaxation and was not associated with marked contracture. Right and left abdominal, cremasteric and Babinski reflexes were present; eyegrounds and papillary reflexes were normal; knee jerks were variably moderate and hyperactive. Spasms of the pharyngeal, lingual and associated muscles made swallowing, mastication, and phonation difficult. There was frequent salivation. The latter characteristics

combined with the motor disability had led a previous physician to a diagnosis of mental deficiency.

Close study revealed, however, that in spite of the handicaps the mental age was close to normal and the deficiency was of a selective, rather than of a pervasive, nature. The boy won for himself a circle of friends among children of his own age, with whom he played; he watched them with avid interest in their play outside his window, obviously wanting to participate. Interpersonal communication was achieved by crude gestures and sounds. During the ensuing years, until the age of 9½, he had desultory schooling. His achievements at the age of 8½ corresponded to those of a child of 6 years. From the age of 9½ to that of 10, his schooling was of a more planned and determined nature, and further gains were made. He showed interest in his work. He could read 100 words, but did not show spontaneous interest in reading at home. After the age of 10, no appreciable change was noticed as far as newly acquired achievements were concerned. Still, continuous emotional and social maturation took place. He learned to play a simple game of checkers and was able to concentrate on it for twenty minutes. He preferred the company of boys of his own age and showed signs of preadolescent bashfulness toward his mother.

The neurologic symptoms had been but slightly ameliorated by physical therapy, which was faithfully continued for years. The athetoid action patterns of the patient at the ages of 7, 10 and 13 were subjected to extensive cinematic study. Cinemanalysis revealed that these patterns, as far as the head and arms were concerned, corresponded closely to the patterns of the tonic neck reflex of an infant of 4 weeks when the patient was 7 years old, and to those of an infant of 12 weeks when the patient was 13 years old. The movements of the patient differed from those of an infant in that they were stereotyped, abrupt and jerky.

Neuropathologic examination revealed lesions in the basal ganglia which were typical of the macroscopic picture of status marmoratus. The changes involved the thalamic nuclei, the putamen on both sides and, less extensively, the caudate nuclei. Histologically, the cortical cytoarchitecture of the frontal, temporal and parts of the parietal lobes showed a marked paucity of ganglion cells, particularly in the third and fifth laminas, while there were few changes of this type in the cortex of the occipital lobes. There were no glial scars in the cortex. Dense glial scars were observed in certain parts of the thalamus. These were usually stellate and small, but occasionally confluent and large. They were most conspicuous in the pulvinar and the ventromedian thalamic nuclei. They showed no predilection for the vascular system. Fine and coarse myelin fibers were observed in the scarred zones. The pallidal nuclei showed only minimal involvement; this was also true of the tuberal nuclei of the hypothalamus, but the periventricular gray matter and the nuclei of Luys were more extensively altered. The putamen was strikingly scarred on both sides, and the caudate nuclei, only slightly less so. There was no evidence that the process was progressively destructive.

In an analysis of their observations, Gesell and Zimmerman point to the fact that integrity of the autonomic and vegetative behavior was preserved to a remarkable degree. Also, in spite of the cortical and thalamic damage, the emotional morale and the affective organization of the patient were normal in their general character and vitality. While vision and hearing were acute and there was no neuropathologic demonstration of damage to the sensory areas for vision and only slight evidence of injury to the hearing center, and while taste, smell, passive touch and sensitivity to pain were normal, the disturbances in the field of sensorimotor behavior were severe. The patient's most fundamental incapacity lay in the mechanisms of prehension, posture and locomotion, though the disablement was perhaps caused chiefly by interruption of the efferent tracts. Thus, even at 6 months of age he showed an unmistakably propensity to reach, even though he had never attained a neuromotor equipment for prehension or for active touch.

In consideration of the relative maturity of social behavior and personality and the relatively high development of the intelligence of this patient, in spite of the

severe damage to the brain, the authors conclude that the tactile-motor elements of experience are perhaps not as important in the development of behavior as is commonly supposed. Interpretation on the basis of the intactness of auditory and, particularly, visual functions hardly explains the propensities and strivings of the boy toward attainments for which he did not have equivalent motor realization, or even possibility of motor execution. The authors infer that insurance factors of maturation brought about neurologic growth in unimpaired regions of the brain, in spite of the fact that these regions were cut off from normal subcortical (tactile-motor) impulses. They suggest that the degree of patterned mental growth in a case of vascular injury to the brain at birth is determined not entirely by the motor disability itself but also by innate endowment and, perhaps, compensatory development. Innate endowment and compensatory response may have some interdependence, so that a superior nervous system will be less affected by a lesion than one of lesser grade. Here, then, is an insurance factor in that the handicapped infant possesses potentialities which work toward adjustment and integration, with optimum utilization of impaired instrumentalities and impressions. These potentialities must be correctly appraised to secure the best result from therapeutic efforts.

ANTHONISEN, Boston.

PSYCHOGENIC HEADACHE. H. WILSON, Lancet **1**:367 (Feb. 12) 1938.

Of 248 patients who were referred to the neurologic outpatient department of the London Hospital, 52 complained of headache as the prominent symptom. Analysis of these cases revealed that there were no localizing characteristics of any psychiatric significance and that "psychogenic cephalalgia" may occur in any type of psychoneurosis. Worry and anxiety precipitated many headaches in the nonneurotic as well as in the neurotic patients, and Wilson believes that it is fallacious to consider the headache of functional origin when "gross signs of emotional instability and fantastic description" are present. Further, constipation, menstruation and sudden muscular exertion did not play a great role in this series. The onset of psychogenic headache was frequently not remembered; in 2 cases trauma was the modus operandi. The pain was variously described as "a sense of pressure or heaviness, a dull ache defying further description, and a sense of throbbing or bursting." Patients reacted differently to the headaches: some showed the *belle indifférence* of the hysterical person, and some, limitation of activities and resulting anxiety. In others there was a feeling of annoyance and resentment. Finally, a few felt that the headache was associated with a "sense of dis-ease, sometimes described as depression, sometimes as causing . . . the fear of illness and death." Since palpitation and gastric disturbances occur in states of anxiety brought on by emotional change as reflected by the autonomic nervous system, headache may also utilize this pattern of response by "functional physical changes." Psychogenic headaches are of five types: Some are brought on by worry; others occur with anxiety states, in which cardiac and gastric symptoms may be present; others are chronic and are associated with signs of emotional immaturity; others resemble hysterical pains without anxiety and obsessional states, and others are true hysterical headaches. The first two types may be helped by "early and reasonable treatment"; the third type occurs in chronic invalids; the fourth can be helped if the symptoms are variable, but little can be done for the last.

KRINSKY, Boston.

Meninges and Blood Vessels

TUBERCULOUS MENINGITIS AND ITS RELATION TO TUBERCULOUS FOCI IN THE BRAIN. D. BERES and T. MELTZER, Am. J. Path. **14**:59 (Jan.) 1938.

Beres and Meltzer made an anatomic survey of 28 cases of tuberculous meningoencephalitis and of 2 cases of tuberculoma without meningitis. In all cases of tuberculous meningitis there was extension of the inflammatory process into the

cortex resulting in foci of encephalitis, which varied in degree from perivascular infiltration to tubercle formation. In a few cases solitary tubercles were observed, but these were not in contact with the ependyma or leptomeninges. When tubercles occurred in great numbers they were due to direct hematogenous dissemination. Large solitary tuberculomas occurred, with or without meningitis. Cortical tubercles which may have been responsible for the coexistent meningitis were demonstrated in only 6 cases. In 11 cases the choroid plexus disclosed the presence of tubercle formation. The blood vessels which were observed during the course of the study presented no changes that differed from those already described by other authors.

EDITOR'S ABSTRACT.

MENINGOCOCCIC MENINGITIS AND ACUTE MENINGOCOCCEMIA: CLINICAL STUDY. C. V. CRASTER and H. SIMON, J. A. M. A. **110**:1069 (April 2) 1938.

Craster and Simon emphasize certain fundamental phenomena, which, when observed at the bedside of the patient, will aid in an early diagnosis of meningococcic infection and the early use of effective therapeutic procedures. A thorough knowledge of the bacteriologic, anatomic and physiologic relations of the meninges and the cerebrospinal fluid is essential for the proper early diagnosis and treatment of meningococcic infections. Meningococcic infections have a low incidence and a high mortality. In the city of Newark, N. J., during the last nineteen years there were 572 cases, with a mortality rate of 44.4 per cent. A petechial or purpuric rash may be considered the specific rash of meningococcemia. A purpuric rash accompanies the petechial rash when the condition is fulminating. The rash occurs before the spinal fluid becomes cloudy and before the onset of meningeal signs and persists after definite meningeal signs appear. In many cases meningococci can be demonstrated by Gram's stain in blood obtained by puncturing with a needle a petechial or purpuric area. Wright's stain may also demonstrate meningococci in blood taken from the skin when no purpuric rash is present. Acute fulminating meningococcemia associated with hemorrhages in the adrenals has been termed the Waterhouse-Friderichsen syndrome. A meningococcic infection attacked 4 children in one family, 2 of whom recovered and 2 died; postmortem examination revealed the pathologic changes typical of the Waterhouse-Friderichsen syndrome. In 3 of the patients toxic encephalitis was secondary to meningococcic meningitis; in such cases striking deviations from the normal mentality attract the attention of the experienced observer. Two patients had initial complaints of pain and tenderness in one joint, necessitating a tentative diagnosis of monoarticular arthritis. Stiffness of the neck and the Kernig sign did not appear until two days after the onset of arthritic symptoms. In infancy, particularly in the first and second years of life, the early signs of meningococcic infection of the meninges do not point to involvement of the central nervous system. They are more likely to suggest an infection of the upper respiratory tract or a gastrointestinal disturbance. After the disease is well established, stiffness of the neck, the Kernig and Brudzinski signs and other meningeal signs appear.

EDITOR'S ABSTRACT.

ONSET AND COURSE OF EPIDEMIC MENINGITIS AS RELATED TO FLUCTUATIONS IN TEMPERATURE AND BAROMETRIC PRESSURE. G. H. GOWEN, J. Lab. & Clin. Med. **23**:385 (Jan.) 1938.

Gowen made a daily study of weather conditions and correlated his observations with the incidence of epidemic meningitis in Sangamon County, Ill., during 1935. In the study of the possible relation of meteorologic alterations and invasion and localization of the meningococcus in tissues, the data for analysis were obtained from the epidemiologic cards available in the Division of Communicable Diseases of the Illinois Department of Public Health. The study confirms the evidence presented by Petersen that the passage of atmospheric fronts is significant for the penetration of the meningococcus. It is probable that bacterial penetration

of tissue is of common occurrence. Unless the organism concerned is of high virulence or the local resistance is low, there probably results nothing more than reticuloendothelial fixation of the invader, with subsequent destruction. In some instances in which the organism so fixed is not destroyed, the occurrence of a sudden pressor episode, meteorologic or otherwise, may cause the fixed bacteria to be mobilized and thrown into the circulation. The effect of the pressor episode correlates with the three stages (localization in the upper respiratory passages, invasion of the blood stream and metastatic localization) in the development of epidemic meningitis. EDITOR'S ABSTRACT.

TRAUMATIC ARACHNOIDITIS. G. G. J. RADEMAKER, Nederl. tijdschr. v. geneesk. **82**:264 (Jan. 15) 1938.

Rademaker maintains that post-traumatic adhesions of the leptomeninges are more frequent than is generally recognized. This is proved by the fact that the complaints of the patients whose histories are reported in this paper were all erroneously diagnosed. Frequently the complaints are interpreted as "compensation neurosis." The author describes 4 cases of traumatic arachnoiditis: The patients frequently complained of headaches or pains in the neck, back or loins, and the symptoms were often aggravated by physical exertion. They sometimes appeared more than a year, or even several years, after the trauma. Other symptoms were sensory disturbances of radicular extension, reflex disturbances and impairment of the motility. The author shows that a correct diagnosis is possible only with the aid of a test with iodized oil. Surgical treatment produces cure or considerable improvement in some patients. EDITOR'S ABSTRACT.

Diseases of the Brain

OLFACTOMETRY IN CASES OF ACUTE HEAD INJURY. PHILIP P. GOLAND, Arch. Surg. **35**:1173 (Dec.) 1937.

Olfactometry was done on 60 patients with acute trauma to the head. In 38 patients the injury was not complicated by such factors as contusions about the nose, colds and changes in the nasal mucous membrane. Three of the 38 patients showed almost complete anosmia after injury to the occipital region of the skull. Injuries about the anterior portions of the head (i. e., without local injury to the nose or fracture through the cribriform plate) seemed to play a secondary role in producing disturbances of the sense of smell. The loss of the sense of smell following injuries to the back of the head or neck was usually ascribed to contrecoup action on the olfactory fibers lying on the under surface of the frontal lobes. A new mechanism of injury is suggested in which the lateral olfactory striae and the tips of the temporosphenoid lobes are damaged by the lesser wings of the sphenoid bone. Three cases are described in which there were injuries to the side of the head. The patient who suffered from direct injury to the parietal and temporal lobes of the brain had higher olfactory coefficients on the side of the injury. The two who had contrecoup involvement of the brain showed higher olfactory coefficients on the side of the injury. Falls or blows on the back of the neck and occiput seemed to be predominant in producing disturbances or loss of the sense of smell. The occurrence of anosmia after such injuries was not infrequent. Injuries to the side of the head may produce disturbances in the sense of smell. In the limited number of cases described the higher olfactory coefficients were obtained on the side of the injury. GRANT, Philadelphia.

ANOSOGNOSIA, IMPERCEPTION OF HEMIPLEGIA. KARL O. VON HAGEN and ELINOR R. IVES, Bull. Los Angeles Neurol. Soc. **2**:95 (Sept.) 1937.

Von Hagen and Ives point out that the term "anosognosia" was applied by Babinski in 1914 to the imperception by a patient of his own hemiplegia, although

the term really implies unawareness of any diseased condition. They report 6 cases in which this symptom appeared. All the patients were women, whose ages varied from 31 to 76. In all but 1 case the hemiplegia was on the left side; the authors state that the case of right hemiplegia is the first to be reported in which anosognosia was associated with paralysis on this side. In all 6 cases there was impaired perception of pain and touch on the paralyzed side, while sense of position was also impaired in at least one of the paralyzed extremities in all the cases (5) in which it was determined. In 4 instances there was conjugate deviation of the head and eyes to the side of the lesion. Homonymous hemianopia was present in 4 cases, and in the 2 in which it was absent there was conjugate deviation of the head and eyes. In 3 cases there were delusions as to the identity of the paralyzed limb. In 2 of these the patient occasionally identified a paralyzed extremity as another person in bed with her. The anosognosia was temporary in 2 cases. In 5 cases the etiologic factor was apparently vascular; in the sixth there were multiple metastatic abscesses of the brain. Postmortem examination in this case revealed an abscess in the right thalamoparietal peduncle, which Von Hagen and Ives consider to be the cause of the anosognosia. Other abscesses thought to play no role in this symptom were observed in the caudate nucleus, globus pallidus, forceps major and hippocampus on the right. In other cases reported lesions have been shown in the temporal or parietal lobe and in the thalamus. MACKAY, Chicago

DISTURBANCE OF BODY SCHEME. ELINOR R. IVES and J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. **2**:120 (Sept.) 1937.

Ives and Nielsen define "body scheme" as the term applied to the concept which a person has of the relations of the various parts of his body to each other. Disturbances of body scheme vary with the location of the causative lesion in the brain and with the psychic makeup of the person affected. When the lesion involves the predominant hemisphere the resultant disturbance of body scheme usually includes the Gerstmann syndrome in some form, while if the recessive hemisphere is affected the disturbance may include denial of hemiplegia (anosognosia of Babinski), forgetting of the limbs on the affected side or delusion of their absence.

In the first case reported, a man aged 42 fell unconscious while at work; he presented left hemiparesis and hemihypesthesia, greater activity of tendon reflexes on the left than on the right and Babinski and Chaddock signs bilaterally. The right pupil was larger than the left. The patient identified his right extremities as his own, but thought that his left arm and leg belonged to some one else. The brain showed an embolic softening in the retrolenticular portion of the right internal capsule, partly involving the thalamus. Other vascular lesions were observed in the centrum semiovale, just lateral to the right caudate nucleus, in and on the surface of the left temporal lobe and over the entire superior cerebellar surface on the left. There were also two small cysticercus cysts of long standing in the left frontal lobe and the right parietal operculum. Only the lesion in the right internal capsule and thalamus was thought to be causally related to the disturbance in body scheme. In the second case, a man aged 66 suffered a sudden attack of weakness of the left side of the body and complained that his left arm felt like some one else's which had been "stuck on." The neurologic findings included hemiplegia, increased tendon reflexes, Babinski and Chaddock signs on the left and left homonymous hemianopia and left hemihypesthesia. There was also arterial hypertension, with enlargement and moderate decompensation of the heart. The patient died of bronchopneumonia seven days after admission. Postmortem examination revealed extensive softening of the entire right temporal lobe, except for the uncus, the whole lower portion of the right frontal lobe, involving the lenticular nucleus but not the thalamus, and a small area in the anterior part of the right occipital lobe. Ives and Nielsen state that in similar cases reported in the literature the lesions have been above the thalamus, in some cases being extremely superficial. MACKAY, Chicago.

MENTAL SYMPTOMS ASSOCIATED WITH TUMOR OF THE BRAIN: STUDY OF 530 VERIFIED CASES. M. KESCHNER, M. B. BENDER and I. STRAUSS, J. A. M. A. **110**:714 (March 5) 1938.

Keschner, Bender and Strauss studied a series of 530 patients with cerebral tumor in order to determine the frequency of occurrence, nature and localizing value of abnormal mental reactions during the course of the disease. No mental symptoms are specific for cerebral tumor. Mental symptoms are almost twice as frequent in patients with supratentorial as in those with infratentorial tumor of the brain. Disturbances in memory are predominantly more frequent in persons with supratentorial than in those with infratentorial tumor. Complex visual and auditory hallucinations are more frequent in patients with tumor of the temporal lobe. Crude auditory hallucinations are most common on the side of the tumor, whether the tumor is located above or below the tentorium. Localized tactile hallucinations indicate that the parietal lobe opposite the side of the hallucination is the seat of the tumor. The most severe and varied types of psychic disturbances are observed in patients in whom the tumor involves both sides of the brain. Psychogenic reactions are determined more frequently by physical or subjective disabilities and the total personality of the patient than by the location of the tumor in any one part of the brain. The pathogenic factors in the production of mental symptoms, in the order of their importance, are (1) involvement of both sides of the brain, (2) increased rate of development of symptoms of tumor of the brain in general, (3) rapidity of the tumor growth, (4) sudden appearance and rapid development of intracranial hypertension and (5) supratentorial location of the tumor. The age, general condition and premorbid personality of the patient modify the quality of the mental reactions to physical symptoms.

EDITOR'S ABSTRACT.

BLOOD BROMIDE INVESTIGATIONS IN PSYCHOTIC EPILEPTICS. LOUIS MINSKI and J. B. GILLEN, Brit. M. J. **2**:850 (Oct. 30) 1937.

An investigation was made of the bromides of the blood of 32 patients who were both epileptic and psychotic. Seven had received 90 Gm. of bromide a day for ten years; the others had received the same daily dose for from four to seven years. Although high levels of bromide were found in the blood (the highest was 275 mg. per hundred cubic centimeters), there were no clinical signs of bromide intoxication in any of the patients. Bromide medication was discontinued for three months, and the patients were again examined. The mental status of each remained essentially the same. There was only a slight increase in the number of epileptic fits in the group. In 8 patients the number of convulsions was decreased.

ECHOLS, New Orleans.

POST-TRAUMATIC PARKINSONISM AND THE EFFECT OF ATROPINE. T. F. MAIN, Brit. M. J. **1**:170, 1938.

Main reports the case of a woman aged 25 who injured the left forefinger with an ax. Five weeks later, trembling of the finger appeared and eventually spread to the entire arm. Because of this tremor and subsequent weakness of the arm, the patient was unable to work for two and one-half years. Complete relief from symptoms was attained by the use of 4.5 mg. of atropine sulfate daily.

Main concludes that his case illustrates the occurrence of parkinsonism following trauma.

ECHOLS, New Orleans.

SIGNIFICANCE OF NEUROLOGIC SYMPTOMS FOR THE DIAGNOSIS OF CARBON MONOXIDE POISONING. H. DIBELIUS, Deutsche Ztschr. f. Nervenh. **145**:131, 1938.

Dibelius stresses the importance of careful neurologic examination in cases of carbon monoxide poisoning. A typical neurologic syndrome is found in cases of this kind: nystagmus, symptoms of involvement of the pyramidal tract, distur-

bances of sensibility and ataxia of the extrapyramidal type. The symptom last mentioned can be found also in cases of slight carbon monoxide poisoning. These symptoms may be of short duration; hence, repeated and careful examination is necessary. Epileptic attacks may occur at the beginning and during the course of the disease. Pupillary disturbances are frequent at the onset, but may be present also in the latter part of the course, when anisocoria and loss of reaction to light may be observed as a sequel to the intoxication.

ADLER, Boston.

MULTIPLE SCLEROSIS IN THREE BROTHERS. H. CURSCHMANN, Deutsche Ztschr. f. Nervenh. **145**:225, 1938.

In the family reported on there were 4 brothers, 1 of whom died of diphtheria at the age of 15 years. The parents showed no signs of disease of the nervous system, nor was there any history of similar trouble in relatives. The first patient, aged 24, the youngest of the three survivors, had been taken ill, five weeks before the case was described, with diplopia. Examination revealed nystagmus, intention tremor and spastic-ataxic gait. The deep reflexes were exaggerated, and the abdominal reflexes were absent. There were ankle clonus bilaterally and a Babinski sign on the left. Examination of the spinal fluid revealed nothing abnormal except a count of 20 white cells. The second patient, the eldest, aged 35, had become lame six years previously. The legs were numb and ataxic, so that he could scarcely walk. There was difficulty in urination. The right hand became unsteady. A few months after the onset the patient was found to have nystagmus, intention tremor and exaggerated deep reflexes. The abdominal reflexes were weak, and the Babinski and Rossolimos signs were elicited. Examination of the spinal fluid showed pleocytosis and a positive colloidal gold curve. At the time the report was written, the patient was paraplegic, incontinent and euphoric and was confined to a chair. The third patient, the middle brother, aged 33, had become ill thirteen years before, at the age of 17. He had a "shock," with left hemiparesis, including the left side of the face. At that time no cause for the hemiplegia was found. The ratio of cells in the spinal fluid was 124/43/6; there was otherwise nothing remarkable. The patient improved rapidly. On examination at the time of the report, gross horizontal nystagmus was noted. The deep reflexes were exaggerated on both sides, and there were Babinski and Oppenheim signs bilaterally. Marked euphoria and scanning speech were present.

PUTNAM, Boston.

POSTENCEPHALITIC HYPERTHYROIDISM AND HYPOTHYROIDISM. H. MANDEL, Deutsche Ztschr. f. Nervenh. **145**:256, 1938.

Mendel reports 2 cases in which symptoms suggestive of hyperthyroidism—tremor, Graefe's sign and an increased metabolic rate—appeared years after an attack of encephalitis, followed by paralysis agitans. In a third case an attack of influenza occurred in 1921 and was followed by sluggishness of movement, dryness of the skin, bradycardia and lack of spontaneity. The basal metabolic rate could not be determined. The spinal fluid showed no increase of protein. The author is inclined to regard this case as an example of hypothyroidism.

PUTNAM, Boston.

RELATIONS BETWEEN MUMPS AND LATER NERVOUS DISTURBANCES. H. LICHTENSTERN, Wien. med. Wchnschr. **88**:130 (Jan. 29) 1938.

Lichtenstern reviews the literature on the later sequelae of mumps and then reports her observations on 664 women and 520 men who were admitted to a hospital for nervous diseases. Of the women 105, and of the men 47, had supposedly had mumps. It was the author's aim to determine whether there are diseases which are especially frequent in patients who have had mumps. She realizes that the number of cases of mumps was too small to allow definite conclusions, but she investigated the possibility of a correlation between a history of mumps and

the development of later disorders. In summarizing her observations, she says that in the patients who had had mumps she noted a high incidence of hepatic disorders, diseases of the gallbladder, infectious diseases, appendicitis, articular disturbances and neurasthenic syndromes. Relative predominance of chronic cerebral or meningeal symptoms, particularly of headache, was not observed. Endocrine disturbances were likewise not especially frequent. In the men who had had mumps, sexual disturbances and arteriosclerosis were even less frequent than could have been expected on the basis of averages. The relatively higher incidence in patients with infectious diseases was to be expected if it is considered that persons who are more susceptible to infections are also more subject to mumps. In view of the presumably different causation of arthritides, their comparatively high incidence is not readily understandable. In discussing the great frequency of cholecystopathies and hepatic disorders, the author says that only hypothetic considerations are possible so far. She suggests that primary impairment of the pancreas during epidemic parotitis may result in secondary impairment of the liver.

EDITOR'S ABSTRACT.

Diseases of the Spinal Cord

ACUTE ANTERIOR POLIOMYELITIS IN NEW YORK IN 1935. ALFRED E. FISCHER and MAXWELL STILLERMAN, Am. J. Dis. Child. **54**:984 (Nov.) 1937.

Fischer and Stillerman present a statistical analysis of 686 cases of poliomyelitis observed in hospitals in New York in 1935. They noted an increased incidence of the disease in older patients, 13 per cent being over 15 years of age. The fatality rate decreased from 12.2 per cent, in the 1931 epidemic, to 2.6 per cent, in the 1935 outbreak. Paralysis, of either the spinal or the bulbar type, developed in only 65 per cent of the cases, as compared with 83 per cent in 1931; 33 per cent were classified as those of the nonparalytic type, and 2 per cent, as those of the encephalitic type. None of the patients in this group received convalescent serum. Of those entering the hospital in the preparalytic stage, only 20 per cent showed paralysis. The temperature was found to be the best criterion of the activity of the disease; analysis of the cell counts of the spinal fluid was not helpful in prognosis. No relation was found between the virus-neutralizing ability of the blood serum and (1) resistance to the disease, (2) the diagnosis of the nonparalytic form and (3) the degree of recovery from the paralysis.

WAGGONER, Ann Arbor, Mich.

PARALYSIS FOLLOWING THE PROPHYLACTIC INOCULATION OF RABIES VACCINE AND TETANUS ANTITOXIN. F. G. LINDEMULDER, J. Nerv. & Ment. Dis. **86**:284 (Sept.) 1937.

The first case reported by Lindemulder was that of a man aged 49 who had previously been normal except for an anxiety neurosis. Daily intramuscular injections of rabies vaccine were started two days after his abraded hand was licked by a dog with rabies. After the twelfth injection the patient began to complain of pains, paresthesias and weakness in the lower extremities. Although the injections were discontinued, a severe polyneuritic syndrome gradually developed in the legs, with pains and tenderness, stocking-shaped analgesia, loss of proprioceptive sensibility and abolition of the umbilical, patellar, achilles and plantar reflexes. In spite of physical therapy there were marked exacerbation and ascent of the signs three months after their onset, with complete flaccid paraplegia, weakness in the arms, retention of urine and appearance of atrophy of the muscles of the legs and the small muscles of the hands. The tendon reflexes disappeared in the arms, while marked pain and tenderness persisted. Two weeks later gradual improvement began in the upper extremities, with slow recovery of power and reflexes. Several weeks later similar improvement followed in the lower extremities, but with increase in spasticity, loss of proprioceptive sensibility and patchy

areas of analgesia. The Babinski sign was elicited on both sides, and absence of the umbilical and cremasteric reflexes persisted. The condition thus gradually changed from marked flaccid paralysis to spastic paraplegia, with atrophy of the muscles of the hand. Repeated examinations of the cerebrospinal fluid revealed in general normal pressure, no subarachnoid block, about 30 lymphocytes per cubic millimeter, a moderate increase in globulin, negative Wassermann and Kahn reactions and a colloidal gold curve of 1112332100. These abnormalities of the spinal fluid were most marked about four months after the onset of symptoms and gradually improved thereafter. All other laboratory tests gave normal results. The final diagnosis was neuromyelitis following injection of rabies vaccine. Three other patients who received injections from the same lot of vaccine suffered no untoward effects.

The second case reported by Lindemulder was that of a man aged 21 who complained of drowsiness and general aching on the fourth day after receiving an injection of tetanus antitoxin into the left rhomboid muscle. On the following day there was local redness, with swelling and tenderness of the lymph nodes in the axillas and pain in the shoulders. Two days later there were paralysis and swelling in the right hand, but the paralysis promptly disappeared. Neurologic examination revealed slight weakness of the left external rectus muscle, slight "neuroretinitis" and paralysis and tenderness of the right deltoid, supraspinatus, rhomboid and serratus magnus muscles. The right biceps reflex was absent, and there was hypesthesia over the right shoulder joint. The spinal fluid was normal except for a moderately positive Pandy reaction and a colloidal gold curve of 1123321000. There was leukocytosis, with a count of 10,600 per cubic millimeter of blood. Two and one-half months later, despite treatment with salicylates and a right angle splint for the right shoulder, there was atrophy with marked weakness of the deltoid and supraspinatus muscles and hypesthesia about the shoulder. Lindemulder states that two important factors in the treatment of patients with this disurbance are avoidance of heat therapy and provision for physiologic rest of the affected parts during the acute stage of the disease. Underwater exercises are probably best after tenderness of the muscles has disappeared.

MACKAY, Chicago.

ASSOCIATION OF TRAUMA WITH PROGRESSIVE MUSCULAR ATROPHY. G. E. F. SUTTON, Brit. M. J. **1**:225 (Jan. 29) 1938.

Little is known about the etiology of progressive muscular atrophy, but its association with trauma in a small percentage of cases has been described by eminent neurologists during the past decade. These authors divide atrophies in such cases into various groups: muscular atrophy localized to the region of the muscles in the neighborhood of the injured joint; amyotrophy following rapidly on the injury and developing on a paralytic background, and slowly developing wasting not preceded by any notable paralytic phenomenon and not associated with sensory troubles or reflex abnormalities. Sutton states that from 1925 to 1934 there were 31 cases of progressive muscular atrophy in the Bristol Royal Infirmary, in only 3 of which did the notes include a history of injury. It is probable that this number would have been higher but for the fact that many physicians do not inquire about a previous history of injury in such cases because its importance is not recognized. There is no evidence in favor of the idea that trauma merely "pulls the trigger" in cases in which there is a congenital predisposition, nor is there any practical support for the suggestion by Thiemn that ascending neuritis occurs, which ultimately involves the anterior horn cells and so produces the muscular atrophy. Localized reflex wasting after injuries of bones and joints is an entirely different condition. The problem under discussion is one of widespread progressive muscular atrophy developing in some cases years after a severe injury. Sutton thinks that one is bound to assume that a molecular disturbance of the brain or cord is occasioned by the injury. A mysterious feature of the disease

is the lack of correspondence between the pathologic process and the symptoms. It is possible, therefore, that degeneration of the Betz cells in the cortex and of the anterior horn cells in the cord may occur several years after the injury, before clinical signs become manifest. This is evidence that trauma is a definite etiologic factor in some cases of progressive muscular atrophy. EDITOR'S ABSTRACT.

ACUTE ANTERIOR POLIOMYELITIS: RELATIONSHIP OF INJURY TO LOCALIZATION OF PARALYSIS. H. L. PARKER, Irish J. M. Sc., July 1937, p. 303.

Parker says that in thousands of cases of acute anterior poliomyelitis observed every year injury has never been given a position of importance in localization of the paralysis. If the site of injury should be considered as the determining factor in localization of the paralysis, an interesting field of abnormal physiology would be opened. It is reasonable to assume that a gross injury to a limb must produce reflex changes in the central nervous system. The problem here is that while the part injured is peripheral, the damage is central. In this connection the work of Hughlings Jackson comes to mind. If it is assumed that the spinal cord is affected by an acute disease, it is reasonable that the part first affected would be that disordered as a result of incoming morbid stimuli. Reflex paralysis, a rare clinical syndrome, has been described by Purves-Stewart. In this condition a more or less trival injury determines motor, secretory and vasomotor phenomena in a limb. The assumption here is that a reflex change occurs in the spinal cord, determining the paralysis. Though cases are admittedly rare, a sufficient number have been reported to make the condition a clinical entity. Some changes must occur in the spinal cord after injury to a limb or other part of the body; whether these play any part in determination of the localization of damage to the anterior horn cells in a patient stricken with acute anterior poliomyelitis remains a problem for future observers. EDITOR'S ABSTRACT.

NON-PARASITIC EXTRADURAL CYST OF THE SPINAL CANAL. THOMAS S. B. KELLY, Lancet **2**:13 (July 3) 1937.

Kelly reviews the 11 cases of this condition on record and adds the case of a boy aged 15 who showed marked motor weakness of the lower extremities, moderate sensory impairment and roentgen evidence of enlargement of the spinal canal, with thinning of the pedicles. The origin of nonparasitic extradural cysts seems to be "an arachnoidal prolongation around the posterior root, herniating backwards through a congenital defect, as a finger-like process." The patient was operated on and made a complete recovery. KRINSKY, Boston.

Peripheral and Cranial Nerves

ATYPICAL FACIAL NEURALGIA. MARK ALBERT GLASER and H. MARLIN BEERMAN, Arch. Int. Med. **61**:172 (Feb.) 1938.

The term atypical neuralgia is used to designate a peculiar boring, throbbing, deep-seated pain over the face and scalp which does not follow the distribution of any of the cranial nerves. It is more or less constant, not paroxysmal or intermittent, but marked by attacks of varying degrees of severity. Two hundred cases in which there was constant facial pain were studied. Surgical treatment of many types had previously been tried without amelioration of the pain. Addiction to narcotics was common. In most of the cases the onset was before the age of 40; the incidence during the third decade was by far the largest. Females predominated in a proportion of 3:1. The pain was bilateral in about 33 per cent of the cases. The distribution of pain followed no segmental pattern but a circular area within the facial vascular supply. The pain was persistent and continuous, and was associated with exacerbations which came on acutely or insidiously. If

an attack had an insidious onset, it gradually increased in intensity, reaching its height in from several hours to several days. It might then suddenly subside or gradually disappear. The severe attacks occurred at intervals of days or months, but during the interim the patient was never entirely free from pain. The constancy of the pain was probably the most essential characteristic of the syndrome. Cold, excitement and fatigue were frequently instrumental in precipitating an attack, which differed from a bout of trigeminal neuralgia in being less intense but of longer duration. No typical trigger zone was found in this type of neuralgia, but tenderness on pressure in the area of the carotid artery and cervical sympathetic ganglia was often present. Sympathetic phenomena occurred in about 50 per cent of the cases. These consisted of lacrimation, injection of the cornea, inequality of the pupils, nausea and vomiting, flushing of the face and nasal discharge.

BECK, Buffalo.

PHENOMENA DUE TO MISDIRECTION OF REGENERATING FIBERS OF CRANIAL, SPINAL AND AUTONOMIC NERVES. FRANK R. FORD and BARNES WOODHALL, Arch. Surg. **36**:480 (March) 1938.

Ford and Woodhall show that various disorders of motility and sensibility which appear in the course of regeneration of the cranial, spinal and autonomic nerves are most easily explained by the assumption that the regenerating axons have gone astray and have formed peripheral connections other than those they originally possessed. This hypothesis is strongly supported by anatomic studies on regeneration, which seem to show that regenerating nerve fibers rarely follow the course they formerly pursued. The mass movements of the face following facial palsy and similar disorders of ocular movements following palsy of the third nerve are explained in this way. Several cases of lesions of the spinal nerves in which there were phenomena attributable to misdirection of the regenerating nerves are described. The auriculotemporal syndrome and the syndrome of "crocodile tears" are given as illustrations of misdirection of autonomic nerve fibers.

GRANT, Philadelphia.

NERVE INJURIES CAUSED BY INTRAVENOUS INJECTIONS OF DEXTROSE. G. B. HASSIN, J. A. M. A. **110**:948 (March 26) 1938.

Hassin observed 6 cases of injury to the large nerve trunks (especially the median) of the upper extremities in the outpatient neurologic clinic of the Cook County Hospital during a period of eight months; in all the injury was caused by intravenous injections of dextrose. The following instructive features in the cases were recorded: predominant involvement of the median nerve, which was regularly affected in all but case 6; prevalent lesion of the sensory nerve fibers (motor disturbances prevailed only in case 6); long duration of the anesthesia, and the obscure mechanism of the origin of nerve lesions of this type. That they are due to the injections there can be no question, but it is doubtful whether they are caused by nicking of the nerve by the needle. The presence of ecchymoses (cases 1 and 5) around the elbow speaks for such an etiologic factor, though pressure by the adhesive plaster in holding the needle in place on the arm or the fixation of the arm against the board combined with the long period of the treatment in the case of patients debilitated and weakened by protracted illness (diabetes) or dangerous surgical states may also be responsible for the neuritic phenomena. The edema or swelling that was present in some cases can hardly be considered a contributing factor, as in other cases swelling was not mentioned. Probably several factors were instrumental in the causation of the lesions and should be borne in mind at the time the injections are given.

EDITOR'S ABSTRACT.

MÉNIÈRE'S DISEASE: STUDY BASED ON EXAMINATION MADE BEFORE AND AFTER AN INTRACRANIAL DIVISION OF THE VESTIBULAR NERVE. S. J. CROWE, Medicine **17**:1 (Feb.) 1938.

Crowe studied 117 patients with Ménière's disease observed at the Johns Hopkins Hospital during the last nine years. In 23 the disease was relatively mild, and no immediate operation was indicated; they have been reexamined from time to time. Ninety-four patients had disabling attacks and came to the hospital for division of the vestibular nerve. The author believes that stimulation of the vestibular end organs is the cause of the sudden, violent attacks of vertigo, the sensation that surrounding objects are whirling and the temporary staggering gait in Ménière's disease. When the central vestibular pathways are irritated by a new growth, the dizziness and incoordination are constant; there is no sensation of objects spinning in a rotary direction, and the periods of freedom from all vestibular symptoms so characteristic of Ménière's disease are absent. In other words, Ménière's disease is a form of aural vertigo that involves the cochlea as well as the static labyrinth. Ménière's disease is a combination of vestibular and auditory disorders. The diagnosis is made largely on the description of the attacks of vertigo. Too much emphasis placed on special examinations (the audiometer, tuning fork and vestibular tests) may lead to confusion. Of the 117 patients, 74 were men and 43 women. Only 10 of 73 patients had a history of otitis media at any time, and only 2 had an infection of the accessory nasal sinuses when admitted to the hospital. Vertigo, the symptom that disables patients with this disease, is always cured by intracranial division of the vestibular nerve. The deafness and tinnitus are only slightly less disturbing.

EDITOR'S ABSTRACT.

PARALYSIS OF THE THORACIC NERVE ASSOCIATED WITH LESION OF THE SYMPATHETIC NERVOUS SYSTEM RESULTING FROM TRAUMA DURING SPORTS. L. GUTTMANN, Deutsche Ztschr. f. Nervenh. **145**:83, 1938.

Guttmann describes 2 cases of paralysis of the serratus magnus muscle, the first of which occurred during boxing and the second after a strenuous period of rowing. In both cases, in addition to the typical symptoms, the shoulder on the side of injury was held in a higher position, and there was homolateral hyperhidrosis extending from the face to the abdomen. Guttmann discusses the possible reason for the hyperhidrosis. It was questionable whether this was caused primarily by an injury to the sympathetic nerve or secondarily by the abnormal position of the shoulder blade in relation to the vertebral column. The prognosis in a case of traumatic lesion of the thoracic nerve is not unfavorable. Movement of the affected arm must be avoided to prevent any further strain on the nerve. Electrotherapy has proved beneficial.

ADLER, Boston.

POLYNEURITIS OF PREGNANCY AND KORSAKOFF'S PSYCHOSIS. P. A. VAN DER HOEVEN, Nederl. tijdschr. v. geneesk. **82**:873 (Feb. 19) 1938.

Van der Hoeven describes the history of a woman aged 30 who for years had exophthalmic goiter. In June 1936 she became pregnant, and emesis developed, which soon assumed the character of hyperemesis. The patient was hospitalized, and her condition improved so that she was able to take food. However, psychic disturbances set in, and the hyperemesis recurred. In view of her poor condition, it was decided to interrupt the pregnancy. At first there was improvement, but the psychic disorder became more severe and the typical signs of Korsakoff's psychosis appeared. Moreover, the patient complained of severe pains in the arms and legs accompanied by formication and severe sweating. Examination revealed reduced strength of the muscles and abolishment of the tendon reflexes. A diet of high vitamin content produced some improvement, but because of persisting paretic conditions, hypesthesia and other disorders, medication with a vitamin B preparation was begun. Under the influence of this treatment the disturbances gradually

subsided. This clinical picture, the author believes, resulted from a deficiency in vitamin B. Further, the induced abortion was a factor in the development of the picture. He suggests that B avitaminosis may play a part in the development of hyperemesis gravidarum.

EDITOR'S ABSTRACT.

Treatment, Neurosurgery

EXPERIENCE WITH SULPHANILAMIDE IN MENINGITIS. JOSEPHINE B. NEAL and EMANUEL APPELBAUM, Am. J. M. Sc. **195**:175 (Feb.) 1938.

Neal and Appelbaum report the results of treatment with sulfanilamide of 17 patients with hemolytic streptococcic meningitis. In all but 1 the disease was secondary to infection of the ear or mastoid. Administration of 10 cc. of prontosil soluble (the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1-hydroxynaphthalene-3′, 6′-disulfonic acid) intramuscularly every four hours, of from 5 to 15 grains (0.32 to 0.97 Gm.) of sulfanilamide every six hours orally and at times of from 10 to 25 cc. of an 0.8 per cent solution of crystals of sulfanilamide intraspinally was employed. Thirteen patients recovered; the fatal termination in 4 patients could not be ascribed to failure of action of the sulfanilamide. Of 274 patients with various kinds of streptococcic meningitis treated prior to the end of 1936, before the use of sulfanilamide, only 15 recovered. Of 14 patients with pneumococcic meningitis treated with sulfanilamide, 3 recovered. The former fatality rate for this type of meningitis was 100 per cent. Sulfanilamide should be used in conjunction with specific serum. In all forms of meningitis it is important to drain the subarachnoid space adequately. The results for meningitis due to the hemolytic streptococcus have been excellent, and those for pneumococcic meningitis encouraging.

MICHAELS, Boston.

INTRASPINAL (SUBARACHNOID) INJECTION OF VITAMIN B_1 FOR RELIEF FROM INTRACTABLE PAIN, AND FOR INFLAMMATORY AND DEGENERATIVE DISEASES OF CENTRAL NERVOUS SYSTEM. E. L. STERN, Am. J. Surg. **39**:495 (March) 1938.

In determining the feasibility of intraspinal injections of synthetic vitamin B_1, Stern made experiments on cats; since then, 120 intraspinal (subarachnoid) injections, in doses of from 500 to 50,000 international units (from 1 to 100 mg.), have been given to 28 patients with inoperable cancer, Recklinghausen's disease, multiple sclerosis, degeneration of the pyramidal system of unknown etiology, thromboangiitis obliterans with pregangrenous condition of the feet, duodenal ulcer associated with pulmonary tuberculosis, alcoholic neuritis of the supraorbital and sciatic nerves, cardiac decompensation, uremia, anuria, tabes dorsalis, hypertrophic spondylitis, osteoporosis of the spine, Paget's disease, intractable pruritus ani and vulvae, beriberi and acute poliomyelitis. The beneficial effects of vitamin B_1 administered intraspinally appear much quicker than when it is given by other routes, because the vitamin remains in the cerebrospinal fluid for several days after a direct intraspinal injection. Improvement in varying degrees was noted in all the patients: All felt and looked better; appetite was increased; pain was lessened or abolished; muscular control, speech and gait improved; the joints became looser; libido was increased, and diplopia was corrected. The patient with multiple neurofibromatosis responded most favorably. In addition to marked general improvement, some nodules became softer and smaller, and some disappeared. Treatment should start with 10 mg. and be increased from every fourth to seventh day, or more frequently in urgent conditions. No patient had any paralysis, anesthesia or signs of meningitis after the injection. Cell counts on the spinal fluid were not appreciably increased. The hydrogen ion reading of the spinal fluid was usually reduced. In all cases in which there is a p_H above 8.5 treatment should be pushed, but it is inadvisable to reduce the p_H below 7, since restlessness and nervousness may ensue. Uncontrolled intraspinal administration may cause "vitamin B_1 poisoning," which, as demonstrated experimentally, may prove fatal.

EDITOR'S ABSTRACT.

SYMPATHECTOMY FOR PERIPHERAL VASCULAR DISEASE. GÉZA DE TAKÁTS, Arch. Int. Med. **60**:990 (Dec.) 1937.

Critical data in the cases of 24 patients who had had 46 sympathectomies were obtained for the purpose of evaluating the objections which have been raised to the use of this operation in the treatment of peripheral vascular disease. First, it has been objected that the peripheral circulation returns to the preoperative level after a short time. Vascular tonus was regained after a brief initial period of vasodilatation. In spite of the recovery of vascular tonus, peripheral circulation was usually much improved. Although the vessels reacted to heat, cold and the metabolic requirement of the tissues, deprivation of vasomotor influences freed them from a number of important extrinsic and intrinsic stimuli which come continuously or intermittently over the efferent sympathetic pathway. Cooling, pinching the body, pain, fright and anger did not produce vasoconstriction in the sympathectomized extremity; heating the body did not cause vasodilatation. Sympathectomy creates rest for diseased and inflamed vessels from central or reflex stimuli. The diseased vessels themselves are responsible for maintaining spasm of the collateral vessels by a spinal reflex which enters the spinal cord through a sensory pathway and emerges as a sympathetic efferent stimulus through the anterior roots. In most patients it is impossible to excise the focus of irritation and thereby interrupt the afferent pathway of the reflex. Sympathectomy interrupts this pathway, thus producing beneficial results.

Second, an important argument against sympathectomy is the regeneration of sympathetic fibers and the restoration of their functional activity. The active lower centers will not be inhibited by higher nerve stimulation because central and reflex stimuli do not reach them. Therefore, the blood flow is more constant and less inhibited than before the operation.

Third, objections are raised that the vascular diseases for which sympathectomy is performed are not specifically diseases of the vasomotor system. None of the material investigated in this study showed histologic evidence of pathologic processes, either in the excised nerve ganglia or in the nerve trunks themselves. The beneficial effects of sympathectomy result from alteration in function after operation rather than from the removal of diseased tissue.

Last, the slight or negligible clinical benefit of sympathectomy is frequently due to the following factors: mistaken diagnosis, mistaken indications for operation, improper stages of the vascular disease and faulty technic.

BECK, Buffalo.

PRESENT-DAY STATUS OF TREATMENT OF NEUROSYPHILIS. P. A. O'LEARY, J. A. M. A. **109**:1163 (Oct. 9) 1937.

O'Leary points out that in 94 per cent of a large group of patients with early syphilis, adequate administration of arsphenamine, bismuth or mercury prevented the appearance of neurosyphilis. When the neurosyphilis was manifested, the value of chemotherapy was greatest in the asymptomatic type, in the early stages of which it produced excellent results in 75 per cent of patients, while it was practically valueless in the treatment of patients who gave evidence of well established dementia paralytica. Between these two extremes are a great number of patients with various types of neurosyphilis, in whom the results of chemotherapy differ according to the duration of the syphilis and the degree and extent of involvement of the central nervous system. In patients with only invasion of the nervous system the results of treatment are usually satisfactory, while in those with extensive parenchymatous and vascular involvement the results are proportionately unfavorable. Accordingly, the demand for a method to control the disease in the latter type was met when Wagner von Jauregg recommended malarial therapy. The effort to simplify malarial therapy resulted in the development of artificial fever therapy. Fever therapy in the treatment of neurosyphilis, although used empirically, should be administered in conjunction with, or immediately followed by, chemo-

therapy. In addition to arsphenamine, compounds of bismuth or mercury and fever therapy, there are several therapeutic agents which are of value in the treatment of neurosyphilis. Outstanding among these is tryparsamide, which when used in conjunction with fever therapy offers the highest incidence of clinical and serologic remissions in dementia paralytica. The combination of tryparsamide and a compound of bismuth is recommended in the treatment of patients with neurosyphilis who are too debilitated to undergo fever therapy, as well as of those who are not benefited by fever therapy. The value of intraspinal therapy is well demonstrated in patients with early clinical signs of tabes or atrophy of the optic nerve and in those with asymptomatic neurosyphilis. The less intensive types of nonspecific therapy—typhoid vaccine, hot baths, sulfur in oil and bacterins—are applicable when a mild nonspecific effect is desired. Many patients, especially those with the early manifestations of neurosyphilis, are strikingly improved by routine therapy, and it is advisable to give them first the benefit of a trial with arsphenamine and a compound of bismuth or mercury. If a favorable response is not obtained after two such courses of treatment, nonspecific therapy should be considered. However, if the patient displays early manifestations of dementia paralytica, fever therapy should be employed immediately. The factors that influence the decision as to the type of nonspecific treatment to be adopted are the type and degree of neurologic involvement, the age and general condition of the patient and the duration of the syphilis.

EDITOR'S ABSTRACT.

TREATMENT OF SCHIZOPHRENIA WITH METRAZOL BY PRODUCTION OF CONVULSIONS. I. FINKELMAN, D. L. STEINBERG and E. LIEBERT, J. A. M. A. **110**:706 (March 5) 1938.

Finkelman, Steinberg and Liebert began the use of metrazol in the treatment of dementia praecox at the Elgin State Hospital on March 1, 1937. Among the 66 patients in their group all types of dementia praecox but the simple were represented. The duration of the psychosis ranged from two months to seventeen years, in the majority of patients being more than two years. No patient who had had the disease more than two years had a complete remission. However, remission with a slight defect could be obtained. The percentage of remissions dropped rapidly, so that after a duration of three years no remission was to be anticipated. The best results were obtained in treating the early stages of catatonic and paranoid dementia praecox. No patient who had been ill less than one year failed to show some response to treatment. The number of injections necessary to produce a remission increased with the duration of the psychosis. For patients ill eighteen months or less the average number of injections was ten and three-tenths, and for those ill more than eighteen months, twenty-five and seven-tenths. Many patients gained weight during treatment. The convulsive seizure produces many changes in the organism, such as anoxemia followed by increased oxygenation, increase in the supply of blood to the brain and increase in the activity of the muscles, with all the chemical changes accompanying such activity. All or some of these factors may be responsible for the remission produced in schizophrenia. There remains, however, the problem of how physical changes in the body cause psychic symptoms to appear and disappear. It was found that 85 per cent of the patients whose symptoms were of less than six months' duration had a remission. Contraindications to this therapy are acute infectious diseases, pulmonary disease and cardiovascular disorders. There were no fatalities, and the only complications encountered were dislocation of the mandible and dislocation of the humerus.

EDITOR'S ABSTRACT.

THERAPEUTIC USE OF VITAMIN B_1 IN POLYNEURITIS AND CARDIOVASCULAR CONDITIONS: CLINICAL INDICATIONS. M. B. STRAUSS, J. A. M. A. **110**:953 (March 26) 1938.

Strauss states that not all polyneuritides and circulatory disturbances of unknown cause are due to vitamin B_1 deficiency. It is possible also that some of

the supposed symptoms of B_1 deficiency in man are in reality due to some other factor, such as riboflavin or nicotinic acid, closely associated with vitamin B_1 in nature. The clinical differentiation of the different types of polyneuritides may be aided materially by the history of dietary deficiencies or conditioning factors, such as alcoholism, pregnancy, diabetes and gastrointestinal disorders. Frequently, however, the differentiation can be made from the clinical examination of the patient. Vitamin B_1 may be employed in pure crystalline form, or substances rich in vitamin B_1 content may be administered. In the case in which there is a definite diagnosis of beriberi, treatment may well be initiated by the intramuscular or intravenous injection of from 20 to 50 mg. of crystalline vitamin B_1 daily. After a fortnight oral therapy may be employed in the same dosage, or, if injections are continued, the dose is decreased to 10 mg. daily until the patient is relieved from all symptoms. Brewers' yeast, plain or autolyzed, serves as a convenient means of administering not only vitamin B_1 but other portions of the B complex. Thirty grams of a powdered brewers' yeast of good potency administered three times daily will generally suffice for treatment of the patients with less serious vitamin B_1 deficiency. Since fatal vasomotor collapse can appear without warning in untreated patients with beriberi heart, it is of utmost importance that the administration of vitamin B_1 be commenced promptly. Deficiency disease in man is seldom limited to a single factor. A diet deficient in vitamin B_1 may possibly be low in other portions of the vitamin B complex as well as in vitamins A and C and iron and other minerals. It is, accordingly, wise to provide that a patient with beriberi receive, in addition to proper amounts of vitamin B_1, an adequate amount of vitamins A and C and iron, as well as food rich in other portions of the vitamin B complex. The dilute liver extracts, suitable for intramuscular injection, given in a dose of from 10 to 20 cc. or more daily, have been particularly valuable in controlling glossitis and cutaneous manifestations of the pellagrous type. The results of vitamin B_1 therapy for both the polyneuritic and the cardiovascular manifestations of beriberi are gratifying. Peripheral nerves are capable of regeneration as long as the cell body in the spinal cord or the posterior ganglion remains viable. Since this regeneration commences at the cell body and progresses distally at a rate of approximately 1 mm. a day, it is apparent that months will be required for the complete repair of advanced degeneration. Therefore, treatment must continue unremittingly until this occurs. Regeneration of completely degenerated cells and axis-cylinders within the central nervous system does not take place. The response of the cardiovascular system to adequate vitamin B_1 therapy is often dramatic. Within a few days the pulse rate is slowed; diuresis occurs, and edema lessens. Within a fortnight the patient may lose 20 pounds (9 Kg.) or more of the fluid; the electrocardiogram may return to normal; the heart may become noticeably smaller, and the vital capacity of the lungs may increase markedly. In deficiency of long duration, anatomic changes may occur in the cardiac muscle, so that five weeks or more may be required for the remission of all signs and symptoms. Repair of neural lesions in most instances occurs at an even slower rate than that of cardiovascular disturbances. Striking as are the results of vitamin B_1 therapy in the cardiovascular disturbances arising from deficiency of vitamin B_1, no effects are to be expected in other types of cardiac disease, with or without edema, in the edema of pregnancy toxemias, nephrosis and the like.

EDITOR'S ABSTRACT.

EFFECT OF VITAMIN B_1 ON PERIPHERAL NEURITIS OF PELLAGRA. T. D. SPIES and C. D. ARING, J. A. M. A. **110**:1081 (April 2) 1938.

Spies and Aring chose 6 cases of classic pellagra for the study of peripheral neuritis. In 4, pellagra had developed after the substitution of the calories supplied by alcohol for the calories ordinarily obtained from food. In the remaining 2 cases the pellagra (the so-called endemic type) was not associated with chronic addiction to alcohol. It has been pointed out previously that the severe peripheral neuritis associated with pellagra usually progresses when the patient is restricted

to a pellagra-producing diet. Irrespective of whether or not the pellagra followed long-standing ingestion of alcohol, the prompt relief from the spontaneous pain of neuritis by the intravenous injection of crystalline vitamin B_1 was striking in all cases. Nicotinic acid administered by mouth in 3 cases completely relieved the severe stomatitis and glossitis and promptly produced healing of all the lesions of the mucous membranes. The observations suggest that the painful peripheral neuritis in these cases was caused, at least in part, by lack of vitamin B_1. The response to the injection of this substance was prompt and dramatic. These studies complement the suggestion offered a number of years ago that the clinical manifestations of the pellagra syndrome are caused by a lack of more than one essential substance. Not all persons with pellagra, however, have peripheral neuritis. While in these cases the pellagrins responded to a basic diet plus supplements of nicotinic acid and thiamin (vitamin B_1), it is not recommended that such a diet be used in the treatment of pellagra.

EDITOR'S ABSTRACT.

TECHNIQUE OF SOMNIFAINE NARCOSIS. DUNCAN MENZIES, Lancet **2**:559 (Sept. 4) 1937.

Menzies discusses the continuous administration of narcotics in the treatment of mental disease and reports on a series of 100 patients for whom this treatment was used. The diethyldiallylbarbiturate of diethylamine (somnifaine), a mixture of barbital in a solution of glycerin, alcohol and water, is usually the drug of choice for this purpose and is administered orally, intravenously or intramuscularly.

Of the 100 patients treated, 34 were discharged as recovered; the condition of 15 was improved, and that of 50 was unchanged. No patient was made worse by the treatment; 5 had a relapse within one year. The following diagnoses were made: dementia praecox, 23 cases; melancholia, 37 cases; mania, 19 cases; paraphrenia, 15 cases, and puerperal psychosis, 6 cases.

The method used by Menzies consisted of the administration of 2 cc. of somnifaine intramuscularly on the first three days of the treatment. This produced three or four hours of sleep. If the patients became restless, paraldehyde was given by mouth or by rectum. An additional 2 cc. was injected on the fourth day, and 4 cc., in divided doses of 2 cc., was given on the fifth, sixth and seventh days, at 2 and 7 p. m. On the eighth day it was usually decided whether the patient needed more than 4 cc. in twenty-four hours. On the basis of the degree of narcosis as well as the patient's general condition, the maintenance dose was arrived at. A maximum of 8 cc. could be tolerated in some cases.

The minor complications which may occur are usually nausea and vomiting, retention of urine and slight elevation in temperature. The treatment is usually continued for about fourteen days, with gradual reduction in the dose from the twenty-first to the twenty-third day, and is concluded in one month. The only indication for abrupt termination of the narcosis in this series was a temperature of over 103 F. with attendant tachycardia.

The claim is made that narcosis can be safely induced with this drug, that there are no clear contraindications and that continual sleep is not essential. Administration of insulin only "adds to the difficulties and anxieties of the narcosis."

KRINSKY, Boston.

TREATMENT OF CEREBRO-SPINAL MENINGITIS BY CONTINUOUS SPINAL DRAINAGE. C. G. K. THOMPSON, Lancet **2**:1242 (Nov. 27) 1937.

Thompson describes a method whereby constant drainage of purulent spinal fluid is possible in cases of meningitis. This is based on the utilization of a special corkscrew type of cannula, which is held in situ by the interspinous ligaments. This cannula is so constructed that frequent specimens of fluid can be obtained and a minimal cerebrospinal fluid pressure of 100 mm. of water be maintained by the use of a reservoir and manometer. The cannula may be held in position for a week and must be inserted with the use of general anesthesia or local anesthesia

preceded by an injection of scopolamine. Twenty-eight patients were thus treated, with a mortality of 14.3 per cent, as compared with a mortality of 28.8 per cent reported for uncorrected methods of drainage.

There are certain advantages and disadvantages of this method. The principle is physiologically sound; serum need not be given intrathecally; repeated lumbar and cisternal punctures, with attendant risks, are eliminated; block does not occur; rapid relief is obtained, and consciousness returns quickly; however, the apparatus is costly; special nursing care is required, and the method is impractical with infants.

KRINSKY, Boston.

EVALUATION OF INSULIN SHOCK THERAPY ON THE BASIS OF PREVIOUS EXPERIENCES. F. BÜDINGEN, Monatschr. f. Psychiat. u. Neurol. **97**:212 (Nov.) 1937.

Insulin shock has been used by Büdingen in the treatment of 56 patients with schizophrenia and 6 patients with symptomatic and manic-depressive psychoses. Complete remissions occurred in 12.9 per cent of the whole group, social remissions in 11.2 per cent and improvement in 19.3 per cent. The term "social remission" was used when there was slight residual defect in a patient who was able to return to his former occupation. Satisfactory remissions were observed in 33.3 per cent of the patients who had been ill for less than six months and in 9.9 per cent of those ill for more than one and a half years. Of the 56 patients with schizophrenia, full remissions were noted in 7.1 per cent, social remissions in 10.7 per cent and improvement in 17.8 per cent. These figures probably do not differ greatly from those reported for spontaneous remissions in schizophrenia. However, the remissions observed by Büdingen developed in relation to the insulin shock therapy, whereas spontaneous remissions were generally reported without regard to the time at which they occurred. Contrary to the observations of Sakel and Müller, good results were not obtained in patients with the paranoid form of schizophrenia. Of 12 patients with this form, the condition of 9 was unchanged, and that of 3 was slightly improved. One patient died after a convulsive seizure, which was associated with a late recurrence of hypoglycemic coma. One patient showed myoclonic epileptic phenomena for thirty-six hours, and another had severe icterus. According to Büdingen, it is dangerous to allow patients to remain in a state of hypoglycemic coma for longer than four hours. In his opinion, the so-called activation of the psychosis represents a condition identical with that often caused by hypoglycemia in mentally normal persons. It is probable that humoral and vegetative changes produced by insulin shock therapy are largely responsible for its favorable results.

ROTHSCHILD, Foxborough, Mass.

THEORETICAL ASPECTS OF INSULIN SHOCK THERAPY AND METRAZOL CONVULSIVE THERAPY OF SCHIZOPHRENIA. L. VON ANGYAL, Monatschr. f. Psychiat. u. Neurol. **97**:280 (Dec.) 1937.

According to von Angyal, the disturbances produced by insulin shock therapy can be differentiated into six fairly well defined syndromes: the frontopolar, the ontogenetic-aphasic, the cenesthetic, the paralogic and sensoroamnesic-aphasic, the staticoparesthetic and the parieto-occipital. The type of prepsychotic personality, the neuropathologic syndrome observed in the early stages of schizophrenia and the type of syndrome produced by insulin shock are definitely related. For example, if a patient with an eidetic constitution acquires schizophrenia, the psychosis will be characterized by complex visual hallucinations, and a parieto-occipital syndrome will be noted during insulin shock treatment. Von Angyal believes that the material substratum of different types of personality is represented by variations in development of the different terminal association areas of Flechsig, one or another area being especially differentiated. Such highly differentiated areas are unusually susceptible to injurious influences and are therefore vulnerable

to both the schizophrenic process and the insulin shock treatment. The various types of syndromes produced by insulin may thus be regarded as schizophrenic focal reactions.

The question arises: Why does hypoglycemic shock have a beneficial effect on the diseased cerebral region? Sakel has shown that the depth of shock is not proportional to the degree of lowering of the blood sugar level. After the sugar content of the blood has sunk to a certain critical level, additional or excess quantities of insulin no longer diminish the sugar content of the blood but cause mobilization of the sugar depots of the organism. A further decrease in the amount of blood sugar occurs only if this protective reaction of the organism is exhausted. The cause of the shock or coma is to be sought not in the hypoglycemia itself but in the progressive mobilization of sugar, whereby all cells of the organism, including those of the nervous system, are deprived of sugar. The cells located in the areas involved by the schizophrenic process show a diminished resistance to this process, partly because of their diseased condition and partly because of their special differentiation. As a result of excessive deprivation such cells show an increased avidity for sugar; hence they take up sugar in great amounts when the coma is interrupted. This acts as a strong metabolic stimulus, which provides a possibility for regression or healing of the disease process. Von Angyal realizes that his theory takes into account only one factor—the effect on sugar metabolism. No doubt the general effect of insulin on the vegetative regulation of the organism also plays a role in the treatment.

The convulsions produced by metrazol begin with psychomotor unrest and conjugate deviation of the eyes and often show additional features which suggest that the frontopolar and prefrontal regions are primarily attacked. In all probability, the drug owes its effect to vasoconstriction followed by vasodilatation, that is, to cerebral anemia followed by hyperemia, though direct action on the nerve cells cannot be excluded. This process has a favorable effect on the cellular disturbances which are still reversible. Apparently, the drug has a selective action, affecting the aforementioned regions to a greater extent than other parts of the nervous system. This view is in accord with the fact that metrazol is especially successful in stuporous states, the pathologic substratum of which is probably to be found in the prefrontal cortical areas.

ROTHSCHILD, Foxborough, Mass.

Muscular System

MYASTHENIA GRAVIS. F. S. KENNEDY and F. P. MOERSCH, Canad. M. A. J. **37**:216 (Sept.) 1937.

In 51 of the 87 cases of myasthenia gravis under review, Kennedy and Moersch could not discover any cause that might be considered as a possible factor in the causation of the disease. In 27 cases it appeared that some infection, such as a "cold," "flu," tonsillitis or pneumonia, played a precipitating part, although the relationship of apparent cause and effect was not always clear. Recurring episodes of myasthenia gravis were frequently preceded by an acute infectious process. The ages of the patients at the time of the first onset of symptoms varied from 10 to 77 years. The greatest number were in the third and fourth decades of life. There were 45 male and 42 female patients. The factor of race had no apparent significance. In no instance was there any evidence of either familial or hereditary factors. There was no close correlation between the occupation of the patient and the situation of the early muscular weakness. There was no special environmental or geographic characteristic. The length of time that elapsed between the onset of the first symptoms and the making of the correct diagnosis ranged from one month to twenty-five years and varied considerably. For the 87 cases this period averaged 4.8 years. The appearance of the first symptom of myasthenia gravis and the appearance of the first objective sign of the disease paralleled each

other rather closely. The ocular muscles were involved in 78 per cent of the cases; the facial and masseter muscles, in 61 per cent; muscles of deglutition and phonation, in 58 per cent; muscles of the arms, in 29 per cent; muscles of the legs, in 24 per cent, and muscles of the neck and shoulders, in 17 per cent. No unusual reflex disturbances were observed in any of the cases. The deep tendon reflexes were occasionally decreased, or even increased, but never absent. The spinal fluid was normal in 28 of the 32 cases in which it was examined. Not infrequently, myasthenia gravis may present itself under the guise of marked general fatigue, but not every state of chronic fatigue is a form of myasthenia gravis. Twenty-seven patients had a complete remission, which lasted on the average 2.2 years. Any accompanying illness exaggerates the existing symptoms and tends to precipitate added myasthenic symptoms. There were 34 deaths. As no therapeutic measure of value or practical or consistent regimen for treating patients was available at the time, this mortality represents essentially that for the untreated disease.

EDITOR'S ABSTRACT.

COCCYGODYNIA AND PAIN IN SUPERIOR GLUTEAL REGION AND DOWN THE BACK OF THE THIGH: CAUSATION BY TONIC SPASM OF LEVATOR ANI, COCCYGEUS AND PIRIFORMIS MUSCLES AND RELIEF BY MASSAGE OF THESE MUSCLES. G. H. THIELE, J. A. M. A. **109**:1271 (Oct. 16) 1937.

Thiele believes that the inefficacy of the treatment of coccygodynia is attested by the numerous forms of therapy which have been recommended. The clinical material used as the basis for his study consists of 87 patients encountered in the practice of nine proctologists. No patients with acute injury, such as fracture or dislocation of the coccyx, are included. The series consists of all the patients in these practices who complained of pain in the region of the coccyx, in the supragluteal region or down the back of the thigh. Some of the patients stated that their pain first began as a sense of weight or heaviness which they at first referred to the rectum. This sensation gradually became more severe, and by the time the patient sought relief he was complaining of severe aching or cramping pain referred to the region of the coccyx, which was more noticeable when he was sitting in a hard chair, particularly when sitting was continued, or when he rose or sat down. Inability to lie comfortably on the back was a frequent complaint, the pain being worse in that position. Lying on the side was preferred by the great majority. Periodic attacks of lancinating, breath-taking coccygeal pain superimposed on the severe aching pain were frequent. There were frequent complaints of tenderness of the gluteus maximus muscle close to its attachment to the coccyx. Coccygodynia was found to be accompanied by spasm of the levator ani and/or the coccygeus muscle in 64 of 69 patients seen by nine observers. Spasm of the piriformis muscle was found in 31 of 33 patients (Thiele's and Wilson's) with pain in the supragluteal region or down the back of the thigh. There is a sound anatomic basis for the causation of coccygodynia by spasm of the levator ani and coccygeus muscles and for the production of supragluteal pain and pain down the back of the thigh by spasm of the piriformis muscle. Of a series of 80 patients with coccygodynia or pain in the supragluteal region or down the back of the thigh who were treated by massage by eight proctologists, 60 per cent were cured; 33.7 per cent had definite improvement, and 6.3 per cent had no improvement. A uniform technic of massage was used for all patients. When the finger is inserted full length in the rectum, lateroposterior pressure will place its flexor surface horizontally across the surfaces of the levator ani and coccygeus muscles, almost at a right angle to their fibers. The fibers of the piriformis are felt immediately beyond the sacrospinous ligament and are touched by the finger tip in such a manner that lateral motion of the finger will stroke lengthwise the portion of the belly of the muscle lying within the pelvis. These muscles are massaged in the long direction of their fibers in the same manner that a strop is stroked by a razor. Massage is begun lightly. The sacrospinous ligament is merely pressed on by the finger in a direction vertical to its long axis. As the patient

makes subsequent visits, massage is made with increasing pressure. If a reaction evidenced by increased pain is evoked, light massage is again reverted to, and pressure is increased as tenderness decreases. If definite improvement does not result after the first four or six massages over a period of a week or ten days, orthopedic or other indicated consultation should be sought.

EDITOR'S ABSTRACT.

ELECTROLYTES IN NUTRITIONAL MUSCULAR DYSTROPHY IN RABBITS. W. O. FENN and MARIANNE GOETTSCH, J. Biol. Chem. **120**:41, 1937.

Nutritional muscular dystrophy was produced in rabbits and guinea pigs by feeding diets composed chiefly of grains and milk products. Analyses of normal and pathologic rabbit muscles showed that nutritional muscular dystrophy is associated with a gain in chlorides, presumably proportional to the increase in interstitial fluid, and a corresponding loss of potassium, magnesium and creatine, presumably proportional to the loss in the number of intact fibers. High concentrations of calcium and total phosphorus were found on analysis of muscles showing histologic evidence of calcification.

PAGE, Indianapolis.

PROGRESSIVE MUSCULAR DYSTROPHY AND VITAMIN C. Y. HIRATA and K. SUZUKI, Klin. Wchnschr. **16**:1019 (July 17) 1937.

Hirata and Suzuki were interested in the relation of vitamin C to progressive muscular dystrophy and studied the vitamin C economy of 10 patients who had the disease in a more or less severe form. Tabular reports of the results of these studies indicate that the patients had C hypovitaminosis. They were given daily from 200 to 500 mg. of vitamin C by intravenous or intramuscular injection. In the course of this treatment examination of the cerebrospinal fluid revealed an increase in the vitamin C content. Moreover, subjective as well as objective improvements could be noticed. The authors gained the impression that the continued oral administration of large doses of vitamin C surpasses in efficacy all other treatments of progressive muscular dystrophy. It exerts an especially favorable effect on the muscular adynamia. Although there is, of course, no regeneration of the already impaired muscle fibers, the muscle metabolism, particularly as regards glycogen, creatine and phosphoric acid and adenylpyrophosphoric acid, is favorably influenced by the vitamin C, and the dynamic power of the muscles is again utilized.

EDITOR'S ABSTRACT.

APPEARANCE AND DISAPPEARANCE OF GUNN'S JAW-LID PHENOMENON (JAW WINKING) DURING REGRESSION OF PTOSIS ASSOCIATED WITH SYPHILIS. K. ASCHER, Med. Klin. **33**:1259 (Sept. 17) 1937.

Ascher says that Gunn in 1883 gave the first description of the jaw winking phenomenon and that about 100 cases have since been reported. The case reported here presents some unusual aspects and throws light on the origin of the phenomenon. A man aged 44 had syphilis, complete oculomotor paralysis on the right side and loss of the pupillary reflexes and paralysis of accommodation on both sides. The patient was subjected to intensive treatment with bismuth compounds and neoarsphenamine and to malarial therapy. After completion of these treatments the patient observed one day that when he opened his mouth and chewed the formerly entirely immobile upper lid jerked upward. After about a week this phenomenon ceased, and the upper lid could be moved voluntarily. Meanwhile, the other signs of paralysis persisted. Ascher points out that in the majority of cases jaw winking (jaw-lid phenomenon) is associated with congenital ptosis. Intravital development of the jaw-lid phenomenon is rare, but what is even more unusual is the fact that it appeared and disappeared in a short time, a peculiarity which never before has been reported. The author points out that the temporary character of the phenomenon contradicts the theory that it is the result of abnormal

connections between the nuclei in which originate the involved nerve fibers. He is inclined to accept as an explanation the existence of innervation complexes which are atavistic and dormant under normal conditions but which become active in case of disturbances in the oculomotor region. He calls attention to other manifestations that suggest a connection between the lifting of the lids and the opening of the mouth (opening of the eyes during eating and opening of the mouth while looking sharply).

EDITOR'S ABSTRACT.

Special Senses

ABNORMAL OCULAR AND PUPILLARY MOVEMENTS FOLLOWING OCULOMOTOR PARALYSIS. M. B. BENDER and S. ALPERT, Arch. Ophth. **18**:411 (Sept.) 1937.

During recovery from paralysis of an oculomotor nerve, the formerly paralyzed ocular muscles may present movements contrary to, or incoordinate with, normal associated motions of the globe and eyelid. For example, in looking down the upper eyelid, which normally follows the globe in its vertical movements, may not descend. Instead, it may retract upward when the globe moves downward. The eye may also undergo internal rotation. A rarer type of abnormal movement associated with looking down is constriction of the pupil which at rest is dilated and inactive to light and in accommodation. Bender and Alpert report a case in which the three types of abnormal movements occurred simultaneously in one eye. The pseudo-Graefe phenomenon, i. e., retraction of the upper lid when the gaze is directed downward, and the abnormal internal rotation due to contraction of the internal rectus muscle are undoubtedly the result of indiscriminate regeneration of oculomotor nerve fibers which during the process of healing pass to muscles other than those which they originally supplied.

SPAETH, Philadelphia.

OCULAR DISTURBANCES ASSOCIATED WITH EXPERIMENTAL LESIONS OF THE MESENCEPHALIC CENTRAL GRAY MATTER. ERNEST A. SPIEGEL and NORMAN SCALA, Arch. Ophth. **18**:614 (Oct.) 1937.

Spiegel and Scala point out that lesions of mesencephalic gray matter produce anomalies of pupillary innervation, disturbances of accommodation and convergence, conjugate deviation of the eyeballs and paralysis of associated movements, particularly in the vertical direction. The pathologic processes producing these symptoms are, unfortunately, usually not sharply limited; the lesion may be a tumor acting not only by localized destruction but by pressure, the effect of which may reach the base of the brain, or it may be an inflammatory process extending to neighboring areas.

Spiegel and Scala made focal lesions in the mesencephalic gray matter of animals. Their experiments showed that stimulation of the central gray matter around the aqueduct of Sylvius, below the cranial part of the anterior quadrigeminal body, produced constriction or dilatation of the pupil, depending on whether the pathway of the light reflex or the descending vegetative tracts originating in the hypothalamus were stimulated. Lesions of the central gray matter in this level produced at most transitory disturbances in the light reflex; usually they caused a transitory stimulating effect on the sphincter of the pupil, which showed a tonic type of reaction—retardation of relaxation after cessation of constrictor impulses or on application of dilator impulses.

The authors obtained conjugate downward movements of the eyeballs by stimulation of the central gray matter below the posterior commissure or behind this level, and upward movements by stimulation in the posterior part of the optic thalamus or in the medial part of the tectum of the anterior quadrigeminal body. The downward movement was often associated with downward movement of the head in the same direction. The system innervating downward movements lies in the vicinity of the pupillary light reflex arc and the descending hypothalamic

pupillodilator tracts; it lies near and dorsal to the point of stimulation for convergence movements. Destruction of the central gray matter in the cranial part of the mesencephalon and the pretectal region induces loss of upward and downward movements on cortical stimulation. A small lesion of this region may be followed by various partial disturbances of vertical ocular movements.

SPAETH, Philadelphia.

ACCOMMODATION AND THE AUTONOMIC NERVOUS SYSTEM. DAVID G. COGAN, Arch. Ophth. **18**:739 (Nov.) 1937.

The active participation of the sympathetic nervous system in accommodation seems necessary to explain certain clinical and experimental phenomena which appear from time to time. Cogan reports a group of 5 cases which seem to support this view. The sympathetic system tends to adapt the eye for relatively distant objects and, as such, opposes the parasympathetic system, which tends to adapt the eye for relatively near objects.

SPAETH, Philadelphia.

CHIASMAL SYNDROMES PRODUCED BY LESIONS IN THE POSTERIOR FOSSA. HENRY P. WAGENER and PAUL L. CUSICK, Arch. Ophth. **18**:887 (Dec.) 1937.

Lesions producing pressure on the optic chiasm present symptoms which are extremely variable. While various bitemporal hemianopic defects are the most frequent and most characteristic changes in the visual field, asymmetric or incongruous altitudinal anopsias and homonymous hemianopias are frequently encountered. Unilateral or bilateral complete amaurosis is ascribed usually to a lesion of the optic nerve and is usually interpreted as evidence of a lesion in the chiasm or the optic nerve anterior to the chiasm. In association with choked disks, defects in the perimetric fields suggesting pressure on the prechiasmal portions of the optic nerves or on the optic chiasm itself are interpreted usually as evidence of a basofrontal tumor, a suprasellar tumor or a tumor of the third ventricle. Ordinarily, such a diagnosis is correct. Occasionally, however, field defects due to pressure on the chiasm are produced by a tumor or an inflammatory lesion at a distance from the optic chiasm.

Wagener and Cusick report a case of tumor of the brain, which early in its course gave signs suggestive of pathologic involvement of the chiasma. Autopsy showed marked dilatation of the third ventricle and considerable erosion of the sella turcica, but no tumor. The internal hydrocephalus was apparently due to ependymitis, which had closed the foramens of Luschka and Magendie.

SPAETH, Philadelphia.

DISTURBANCES OF TASTE OF OTITIC ORIGIN, WITH ESPECIAL REFERENCE TO OPERATIONS ON THE EAR. W. Y. H. HO, Arch. Otolaryng. **26**:146 (Aug.) 1937.

Ho studied disturbances in taste of otitic origin that occurred in patients from the otolaryngologic service of the Memorial Hospital, Worcester, Mass., including 4 from the Worcester City Hospital, from December 1936 to May 1937. Especial reference was made to patients who had had operations on the ear, particularly radical mastoidectomy. In a group of 21 patients with acute disease of the middle ear there was no change in the sensation of taste, the reason being that the chorda tympani nerve was not affected either by the acute disease or by the surgical procedure. Of 18 patients in whom chronic suppuration of the middle ear developed, changes in the sensation of taste were noticed by some and not by others. This difference depends on two factors—the resistance of the chorda tympani nerve to the infection and the effect of the pathologic changes of chronic otorrhea on this nerve. Many patients with aural cerumen were questioned, but none was observed with a change in the sense of taste of otitic origin. In the only case of ossiculectomy in which a follow-up study was possible, the patient showed a change

in the sensation of taste on the anterior portion of the tongue corresponding to the side of operation, indicating that the chorda tympani nerve had been injured, owing to its close anatomic relationship to the malleus and the incus. In a group of 17 patients who had undergone radical mastoidectomy in which the chorda tympani nerve was destroyed, the sense of taste on the anterior two thirds of the tongue on the side of operation was invariably absent. Loss of taste was present in 3 patients with paralysis of the facial nerve following mastoidectomy. A change in the sensation of taste was present on the anterior portion of the tongue on the side of operation in 2 patients after modified radical mastoidectomy. This disturbance of taste, instead of complete ageusia, must be attributed to a change in the chorda tympani nerve. In cases of disturbance in taste of otitic origin the patient has no consciousness of any such change; yet clinical tests for taste bring out the loss.

EDITOR'S ABSTRACT.

Society Transactions

PHILADELPHIA PSYCHIATRIC SOCIETY

BALDWIN L. KEYES, M.D., *President, in the Chair*

Regular Meeting, March 11, 1938

SYMPOSIUM ON THE PSYCHOPATHIC PERSONALITY

DEFINITION OF THE PSYCHOPATHIC INFERIOR PERSONALITY. DR. BALDWIN L. KEYES.

In order that the discussions may be clarified, "psychopathic inferior" persons may be defined as those who habitually or from birth are abnormal in emotional reactions and general behavior but who are not psychotic and show no intellectual defect. That is, they may have average, normal or subnormal intelligence, but they have no moral ethics and may therefore be called "moral imbeciles." These patients are wholly unreliable, act on impulse, demonstrate poor judgment, select unwise activity and never learn by experience, so that they will continue to repeat the same offense. They are easily led into paths of crime; they are usually dependent and unable to manage their own lives adequately; they cannot accept responsibility or plan ahead; they are entirely inconsiderate of others. Under institutional conditions these patients usually accept the situation well. They learn trades indifferently, but usually show some community interest and make comparatively good records in the training schools so long as they are supervised and carefully guided in groups. Occasionally, though rarely, some of these patients become psychotic, and many types of psychopathic personalities are recognizable. Now and again, an effort is made to liberate one of the psychopathic patients from the hands of the law on the basis of schizoid tendencies, though it must be recognized that it is normal for this group to show low emotional tone and not unusual for them to manifest schizoid and impulsive behavior. It is important to recognize that these patients know right from wrong, although their conduct is impulsive and not based on good judgment. They are nevertheless held accountable by the law for their actions.

POINT OF VIEW OF THE INSTITUTION. DR. ARTHUR W. PHILLIPS, Huntingdon, Pa. (by invitation).

The population of the Pennsylvania Industrial School, Huntingdon, can roughly be divided into three categories: (1) the intellectually normal, (2) the intellectually defective and (3) the psychopathic.

POINT OF VIEW OF THE LAW. HON. CHARLES L. BROWN.

My associates and I at the Municipal Court have always had to deal with the psychopathic delinquent person in a practical way. A prisoner stands before the court for sentence. How does the court look on him—subjectively or objectively? Too often objectively, I am afraid, for such has been the philosophy of the legal system. The court can, in most instances, have no idea of the processes at work in the mind of the delinquent person. His mental machinery, his heredity and environmental influences are unknown to us.

There is much which cannot be learned in the course of trial. The testimony is made up of the defendant's deeds, but the influences, the environmental and mental kinks, are all "immaterial" testimony and have no place in the legal system. However, in justice to that system, it may be said that even if such evidence were

admitted it would be treacherous, for even if the prisoner were privileged to reveal his inner self I doubt whether he could do so. The prisoner might well do himself injustice. He might be cunning; he might be honest, and, again, he might be only emotional. Truth, then, is weighed on delicate scales, and, for reasons other than are customarily assigned, justice may be blind. One can see, therefore, the straitjacket in which the prisoner as well as the court find themselves. We have learned, however, through pragmatic experience that this background of influences, emotions and mentality is of great importance, especially in the cases of social delinquency.

However, the fact remains that problems such as these have not hitherto had great weight in the minds of jurists, who have been unequipped through want of training in this extralegal domain and through lack of scientific study. Such an all-embracing background is important, even to the jurist who approaches his work in a humane fashion. Indeed, some jurists are inclined to look on medical experts as trespassers. Society still demands a measure of capital punishment for all categories of crimes. The existing system of jurisprudence is built on the philosophy of crime and punishment rather than, as it should be, on that of crime and cure. It is not desired to understand what the prisoner did as much as to know what he did. The antithesis is "understand" and "know." The legal profession has operated without its handmaiden, the sciences. The law has been so limited and circumscribed by rules of economy and modus operandi that it is played as a game is played.

I must confess that perhaps we of the legal profession have been too practical. It is, indeed, this allegedly "immaterial" evidence that we are now beginning to realize is most material if our object is to correct, and not merely to sentence, the offender. More and more, I am sure, will the "immaterial" evidence of psychiatry enter the courtroom. I can see clearly that the jurist of the future will be not merely a jurist qua jurist but one learned in the social and medical sciences. In the field of psychopathic delinquency he will be, in the sense I have defined, more than a jurist. In this connection, I cannot but think of Conrad's "Lord Jim." The story portrays one of the most vivid pictures in literature of the psychologic basis of action. Lord Jim was a mate on the ship "Patna," carrying a cargo and about 1,500 praying pilgrims as passengers. One night, out of the great calm and peacefulness of the sea, a squall came up, bringing with it terror and confusion. The crew suddenly realized that the ship was in imminent danger of sinking. After a few harrowing moments, the captain and crew manned the lifeboats and abandoned the ship and its cargo, including the passengers—all except Jim. He remained on the ship, at his post.

The cowardly crew, giving up Jim as a hopeless fool, shouted to an officer who had died of a heart stroke during the few moments of excitement: "Jump! jump! jump!" Jim looked at the great mass of humanity lying on the deck of the ship, whom he already visualized as dead men. The words "jump, jump, jump" hypnotized his brain. In the confusion, the darkness, the rain and the storm he lost all sense of awareness and jumped. When, a moment later, he found himself lying on his back in a dory, with two broken ribs, he looked up at the vast hulk of the ship and saw that it was impossible to climb back; he already regretted a step which, even to him, seemed impossible. As he later stated: "Let them go through that kind of thing before they talk. Just let them—and do better—that's all." By a strange quirk of accident, the ship did not founder. At a subsequent inquiry, at which Jim alone had the courage to present himself for cross examination, he tried to describe what had happened. Conrad explains that the tribunal wanted facts. "Facts! They demanded facts from him, as if facts could explain anything." To the numerous questions Jim gave impatient answers. He wanted to explain his feelings, his emotions, the scene on that dark, stormy night, as it took place, but the commission wanted only facts. They were right; Jim had jumped. . . . He had deserted the ship. "I had jumped . . . it seems," he added. This he confessed, but he could under no circumstances

explain to the satisfaction of these men how and why he did it. Indeed, one of the dramatized versions of this story has a spectator exclaim at the trial: "Why do they torture him? Why do they seek to judge a man's soul by his action?" I will leave it to those present to draw their own conclusions from this story.

Now, what does all this mean, translated into practical terms of the work at the Municipal Court? It is true that we are bound by legal and other limitations. We have not the power to sentence a delinquent person for an indefinite time or, in some instances of evident mental disorder, for life. Not every one who commits an offense is "insane." The law places definite limitations on our power of commitment, perhaps wisely. Again, the authorities of the institutions to which the subjects are sent may, after a time, act favorably on petitions for parole in cases of apparent adjustment. The law gives them that power; we have not the right of veto. There is still a third limitation with which we have to cope, but which may some day, when the public conscience is awakened, be overcome. Our correctional and curative institutions—Glen Mills, Sleighton Farm, the Pennhurst Training School, the Philadelphia Hospital for Mental Diseases, the Fairview State Hospital and others—are much too crowded. We commit persons with obstinate conditions, but can find no place to which to send them. These are some of the practical, as well as legal, limitations we must face every day.

However, we of the Municipal Court, in our social departments—the Juvenile, the Domestic Relations, the Unmarried Mothers, the Women and the Men Misdemeanants—have recognized, in common with the medical profession, what has been well said in an early report of our court: "At the bottom of all unhappiness or derailment, of all problems of conduct, there is the 'emotional life' of the individual, with all its legitimate and perverted expressions."

There is the problem not only of purely mental disease but of behavior, personality and mental deficiency apart from disease. With every disturbance of one's inner life there is usually a resultant disturbance of social relations. We are trying in our court to deal with both aspects of legal psychiatry. In short, our aim is to approach the problem of the psychopathic delinquent person from the emotional point of view, as well as from the purely factual standpoint, as represented by the accomplished act.

Early in its history the Municipal Court established a medical department to complement its legal functions. Each case is studied from every angle by a person trained in a special field of work. A prisoner is given a physical examination to determine the existence of health deficiency which may have contributed to the delinquency; he is also examined by a psychiatrist, who tries to fathom his emotional history and mental equipment; a study is made of his hereditary and environmental background. The results of all this preliminary investigation are then written up and presented to the trial judge as part of the record in the case. The attempt is then made to fit the sentence to the circumstances and the social purposes sought to be accomplished rather than purely to the crime. What this means to the defendant in terms of rehabilitation and to society need not be labored here. In that way, we hope we are fulfilling the mission of justice in its broader sense. In our efforts to encompass all this, we recognize our debt to the medical profession, and we look forward to its contributions in this important field of medical jurisprudence.

RETURN TO THE COMMUNITY. DR. LOUIS N. ROBINSON (by invitation).

In view of the auspices under which this meeting is held, I think it fair to say that I am neither a psychiatrist nor a psychologist. I was trained as an economist, but after ten years of college teaching I found the field of crime much more attractive. I now divide my time between business and attempts at prison reform. About thirty-one years have passed since I started out to learn about crime and criminals, but I confess that in spite of all the time I have spent I do not know much about either. I am now serving as chairman of the Board of the Prison Industries Reorganization Administration, and most of what I have to say is the

result of an effort to think through situations which I have met in connection with the work of this organization.

This board came into existence in September 1935, by executive order of President Roosevelt. It is primarily a service organization, which the individual states or their political subdivisions may use if they think it can be of service. It is authorized to make studies and surveys and reports directly to the president of the United States. The following states have asked the board to study their prison situation: Vermont, Delaware, Maryland, West Virginia, Kentucky, Tennessee, Arkansas, Oklahoma, New Mexico, Texas, California, Oregon, Utah, Idaho, Wyoming, Missouri, Georgia, Kansas, Nebraska, Indiana, Pennsylvania and the District of Columbia. Studies have been completed in all but six of these states.

The situation in these states presents a bewildering variety of details. One of the representatives of the board visited a reformatory for adults a short time ago. In conversation, he asked the psychologist if he did not sometimes feel the need of a psychiatrist in dealing with the young men committed to the institution. "We sure do," he said. "Why just the other day one of the men fell down the stairs and hurt himself, and we should have had a psychiatrist here to rub his back." In the same state a group of 50 or more prisoners suffering from psychoses were confined in what had formerly been the women's division of the state prison. I happened to be present at the dinner hour. They were seated at a common table, surrounded by five or six prison guards of the usual character, carrying clubs. On inquiry, I found that this group of prisoners had not been visited by a physician for over a month. The governor of the same state argued determinedly for his right to remove all officials of institutions, down to the last janitor—all in the name of efficiency. A few years ago I accepted membership on the board of a large penal institution and urged on them the desirability of appointing a psychiatrist. One member of the board, since deceased, persisted in stating that he saw no reason why a psychopath should be appointed to the staff of the institution; this was the nearest he could come to understanding what I was talking about.

In connection with the work of the Board of the Prisons Industries Reorganization Administration I visited two states, one of which contained one state prison and the other two. Neither had a reformatory for adults or knew anything of adult probation. The parole work was inadequate, with practically no supervision of released prisoners. The institutions were horribly overcrowded, containing a large number of prisoners who should never have been committed to such institutions. I wish to say to those who are interested in psychiatry and psychology that the fields in these two states were ripe to the harvest. I am glad that one of these states has since taken great strides in the right direction, having passed a probation law for adults, built up the parole service, started to build a new institution and employed a well known psychiatrist to assist in the work of administering its two prisons. In looking back over my visits to the state institutions of the states in which the board has worked, I fail to recall meeting more than one or two psychiatrists or psychologists actively associated in the work of handling the men.

In the eyes of the law a man is a criminal who commits or does not commit some act that the law says he must not or must commit. There are a tremendous number of these forbidden acts, varying from petty theft to murder, often wholly unlike in character. The fact that John Smith commits one act and Tom Brown another makes them both criminals, but does not make them alike. It has been proved that no two criminals have exactly the same fingerprints; it could also be proved that no two criminals are alike in character and personality. Slowly and gradually, the state is coming to realize this fact and is attempting, in a halting and vague fashion, to revamp its institutions and agencies for dealing with criminals in the light of this really revolutionary principle.

In the early days all terms of imprisonment were served in county jails, workhouses or houses of correction. Shortly after the time when the move took place to restrict the number of crimes for which death was the penalty, state prisons

and penitentiaries began to be built for those who committed serious crimes. About the same time, authorities came to the conclusion that children should not be sent to jail, and separate institutions for juvenile delinquents slowly came into being. About 1870 the adult reformatory movement started, and about the same time it occurred to some of the states to take psychotic prisoners out of the penal and criminal institutions and place them in special institutions. A few states have begun to remove the feebleminded prisoners from the general prison population and to care for them in a separate institution. Many children and many adults convicted of criminal offenses are now placed on probation, and a large number of persons finish their terms of imprisonment outside prison walls.

I wish that I could say that all states have arrived at this stage of evolution, but this is not the case. Progress is spotty. I have called attention to states which had no reformatories for adults, no probation system for adults and no adequate parole; states the institutions of which were in some instances horribly overcrowded and offered, I am sorry to say, little of educational or reconstructive value. The sorting process has scarcely begun. Prisons are filled with heterogeneous masses of human beings, all made to conform more or less to one kind of discipline, regardless of whether it is suited to those who must submit to it.

Roughly, what is needed is to push forward the notion that a state must have a variety of penal and correctional institutions and agencies to deal with the infinite variety of human beings who commit crimes. I realize, of course, that this, if carried to the logical extreme, would mean complete individualization of punishment, or treatment, if this word is preferred, and would be so costly that no state could afford it. Nevertheless, this is the plan which must now be adopted if this work is not to fail completely. In the past, institutions have been built to serve geographic divisions of a state. Henceforth, they should be built to serve special groups of prisoners. As I said before, the term "criminal" does not mean anything. It is a useless label.

In building institutions the whole thought has been that of security. This idea has outweighed all others. Almost nothing has been known about the persons who were to be kept in the institutions or what was to be done with them except to hold them in one spot. A manufacturer who did not know the kind of material that was to pass through his factory or had no knowledge of what he was to make out of it would be considered mentally incompetent. But prison commissions, and prison architects as well, have had little more knowledge of their job. The prisons contain many feebleminded persons, many of whom, if not actually, are well on the road to becoming psychotic. Many are emotionally unbalanced; many are in need of long, continuous medical treatment; many could profit from an education, and many should be kept apart from society for the rest of their lives. The institutions and the management of these institutions reflect only in a vague way the facts which I have cited about the human beings who live in the prisons.

Here and there one notes a more realistic attitude. The state of Indiana is thinking of building additional institutions. The Board of the Prison Industries Reorganization Administration was asked specifically to consider in its study of the existing situation in that state the examination of inmates of the state penal institutions. There were added to the staff of the board a psychologist, a psychiatrist and a social worker, who, with the assistance of the members of the staff of the Indiana State Reformatory, have been studying the population of the state institutions of Indiana to determine the kind of institutions that Indiana should build. In Washington, D. C., at the request of the authorities, the board has done something of the same kind, utilizing a psychiatrist who was borrowed from the office of the Surgeon General of the United States Public Health Service and a psychologist who was loaned by the prison service of New Jersey. This, I insist, is the way to go about reconstructing penal and correctional systems. One must know the kind of persons to be dealt with and must have at least a general idea of what it is planned to do with them. I am firmly convinced that the psychiatrist and the psychologist have a great part to play in this task. They

must first help in determining the kind of material with which one has to work, and then they must be able to tell how to handle this material.

I do not for a moment believe that all prisoners are simply good boys who have accidentally been led astray. On the contrary, I am convinced that not all the psychiatrists and psychologists in the United States could reform some of the prisoners whom I have met so that they would be decent, law-abiding citizens. Nature has done its work too well. The point, however, is that in too many states prison walls have succeeded in keeping out all scientific endeavor to deal intelligently with those who are confined therein. I do not believe that one can realize fully the truth of this statement. I have visited state prisons which make no tests for venereal disease at the time of admission—institutions the hospital facilities of which are cramped and almost unworthy of the name. A local physician may be summoned to treat a man who is obviously in great need of medical attention. I could mention institution after institution where there are no facilities for dealing with abnormal personalities, or even for bringing out the best in the so-called normal man. Think how far such a state has to go before tolerating the notion that a psychiatrist or psychologist could be of any service in handling prisoners. I have appeared before many legislative committees in Pennsylvania on bills relating to the care and treatment of offenders. Any mention of the term psychiatrist, psychologist or social worker in bills of this character was strictly taboo, unless one was willing to risk having his pet bill laughed to scorn on the floor of the house or the senate. It seems unthinkable that one should not utilize inside prison walls all that the sciences concerned with human behavior can contribute.

A word about parole: This method of dealing with criminals has been condemned roundly, and few have thought to inquire what was wrong with it. It is impossible to do good work with men on parole unless the institution has done its work well while they were confined in it. The first step in good parole work is good institutional work. Why turn over to parole agents men who have never had anything done with them or for them in the years they spent behind walls? Everything that I know about prisons and prisoners points conclusively to the need of enlarging the prison staffs to include trained educators, trained social workers, psychologists and psychiatrists. In a way, the cart has been put before the horse in developing a parole system, when perhaps the whole effort should have been spent on improving the prison system. I warn, however, that an institution which does good work with its men will not wish to hand over the men to the care of an incompetent parole staff. Good work in the institution must be followed by good work outside. If the institution demands the kind of workers that I have mentioned, it will be found necessary to remake and reorganize the staff of most parole bureaus.

In the United States, intelligence has been focused on exploiting natural resources and making money. The results of that policy are now apparent. If there is to be a common life that is safe and interesting, much more time must be spent on the agencies and institutions that govern the common life. Many of these are truly out of date and should have been changed or discarded years ago. As I see it, this is the task of the present generation: to bring these up to date and to the same degree of efficiency that is manifested in the best business organizations. The trips which I have made around the country have produced in me a spirit of optimism. I note that many politically minded men are now finding it worth their time to go before the people of their community with a plea for better penal and correctional institutions and agencies. Two governors come to mind—Governor Chandler, of Kentucky, and Governor Rivers, of Georgia, both of whom have found it to their political advantage to make common cause with prison reformers.

DISCUSSION

DR. SAMUEL LEOPOLD: I was asked to discuss the psychopathic personality as a problem in the Municipal Court and also as a problem of parole at the Eastern State Penitentiary. Let me consider only the problem of the so-called psychopathic

offender in the court. If one looks at the annual report of the Municipal Court, one will find that the psychopathic criminal constitutes the greatest menace in the community and the problem most difficult to solve. There are no facilities either in the city or in the state for handling this problem. The Municipal Court for over twenty years has wrestled with the problem that the state is now encountering and working on. At first, the psychopathic offender was turned over to the probation officers to handle. They worked year after year with the group without knowing why they failed, until it was pointed out by the medical department that the psychopathic offender requires segregation. This when accomplished in part relieved the large load the case workers were carrying. It was a step in the right direction, but the court and the workers were confronted with a still more difficult problem. None of the present institutions, except that at Huntingdon, cared to take psychopathic criminals.

The court is endeavoring to recognize persons of this type earlier and to send them to institutions for training. It is blocked by the lack of such places. The recognition of psychopathic personalities, at least at an early age, is not easy and presents in itself a difficult problem.

DR. PHILIP Q. ROCHE: Considerable discussion of the problems of penal management and parole has appeared recently in newsprint. Many suggestions have been put forth, perhaps by as many protagonists. It is said that there is great need of revamping the system within the commonwealth. The aims of those who have set forth their views have been in common, albeit their approaches have been from different angles.

The Eastern State Penitentiary, with its 3,000 inmates, presents a special problem in itself in relation to the diagnosis, segregation and rehabilitative treatment of the psychopathic personality. On the basis of available case work, it is not possible to make an accurate statement of the number of psychopathic persons now within the prison walls, nor is it easy to classify further the remaining population into the various categories of psychiatric interest. The reason for the inability to provide these data is that there has never been set up a definite scheme of psychiatric classification in the present case work program. However, from comparison with the statistics from other institutions of comparable size and from my own file, I should say that about 20 per cent of the present prison population falls into the category as defined tonight. No special or intimate study on this group of inmates has been attempted. I mentioned these facts in order to point out by way of caution that the best intentions in bringing about a scientific penal program in the commonwealth may easily be defeated if there is not first laid down a well planned outline of procedure—a classification in which there are agreement on terms and uniformity of thinking in regard to the special conditions under which judgment in diagnosis and prognosis is to be based. Until such a foundation of classification is created, it will be extremely difficult to make proper plans for the future policy of penal management. Within recent months there has come to the authorities of the penitentiary the request for an estimate of the number of so-called defective delinquent persons within the prison population. By necessity, the reply to this request was a conjecture. There were no available statistics on the number of defective delinquent prisoners because there has never been set up any definition in the prison administration as to what constitutes a defective delinquent personality. This immediately raises the question as to the wisdom of making plans for the future, especially with respect to the building program in the state, without first having an intimate knowledge of the actual needs for specific building. Returning to the question of the psychopathic personality: It need hardly be emphasized that the psychopathic personality constitutes the most vexatious problem concerned with parole. This problem is exemplified in the statement of Sheldon and Eleanor Glueck, in their recent monograph, entitled "Later Criminal Careers," that the most "marked difference between the reformed and unreformed lies in the factor of mental or emotional difficulties, as evidenced by the finding that only 15.2% of those who reformed were burdened with some psychiatric condition as opposed to 89.9% of those who continue to be

delinquent or criminal." They further stated that "the benign influence of aging on the maturation process may be delayed, blocked or distorted if a delinquent is burdened by a make-up termed by psychiatrists 'psychopathic personality' or 'constitutional psychopathic personality.'"

After an analysis of 500 later criminal careers, the authors expressed the opinion that "only within the factor of aging was a significant explanation to be found for the increasing trend away from criminal conduct." This statement suggests that there should be imposed longer terms on this group of criminal offenders: that if, by means of an indeterminate sentence, a person is held long enough, the mere fact of his growing older will tend to promote his rehabilitation and reform. However, before such judgment is to be passed on the individual offender and he is deprived of liberty, one must have clearly in mind the standard of diagnosis and classification. Such a standard is imperative, in order that one may gain sufficient experience to promote and cultivate other factors, besides that of aging, which will serve to bring about the reformation of the psychopathic offender and, at the same time, cut down the huge expense of long term incarceration. Under present conditions of imprisonment, a healthy program of rehabilitation for the psychopathic group is virtually impossible. It is more probable that under existing conditions the psychopathic prisoner is irreparably damaged. The atmosphere of a compressed prison population composed of a polyglot, unidentified, discordant mass of human beings of all temperaments and ages has little to offer in wholesome channels of reformation.

Dr. Phillips' remarks are well taken, particularly with respect to the initial segregation of the group one prefers to call defective delinquent and psychopathic persons. The difficulties of solving the present problem of segregation should find partial solution in the establishment of presentence segregation through the channels of psychiatric examination.

The diagnosis of the psychopathic personality should be available before sentence in order that the committing judge may be assisted in the disposition of the offender. Thus, a large measure of the present day irregularities of sentencing and parole should find remedy. It should be apparent to every one that the commonwealth cannot project a building program until the composition and requirements of treatment of the penal population are at least statistically determined. It should also be apparent that such an analysis of the composition of the prison population and the requirements of treatment is unattainable until the commonwealth adopts standards of classification. At present there does not seem to be any indication that it will do so. Thus, there is being constructed an "Alcatraz" at Mount Gretna, Pa., intended for the intransigent criminal whose supposed threat of escape is measured by architects in terms of yardage of steel and concrete. Yet, in contrast, the more dangerous "criminally insane" prisoners are held in restraint by no more than wooden doors and latch keys.

In summary: The commonwealth should adopt a statewide plan for psychiatric participation in case work; a standard of classification should be adopted, and there should be created psychiatric services for presentence.

DR. HENRY I. KLOPP, Allentown, Pa.: The care of psychopathic persons is important and is becoming more so. I agree that the only suitable place is an institution for mental diseases. Nevertheless, the question has arisen repeatedly of their being cared for in institutions for defective delinquent persons. The statement has been made that it cannot be done. It is gratifying to learn what is being done in the Municipal Court. The judges are becoming more and more progressive. They are learning that psychopathic offenders need observation and study. This is evidenced by the fact that certain judges take advantage of the provisions of the mental health act and send the offenders to state hospitals for observation, diagnosis and treatment. This applies particularly to children under 16 years of age.

COL. A. H. PIERCE: Within the limits of the definition of the constitutional psychopathic personality, as outlined by Dr. Keyes, I wish to consider the problem

in a broad way. What is the constitutional psychopathic personality? It is a personality with a constitutional flaw. On that basis, it seems that the problem is fundamentally one for the medical profession and for the psychiatrist. Examination and determination as to the existence of a constitutional psychopathy should be made if possible before trial—certainly, before sentence. If existence of such a condition is determined, the person should be committed to an institution in the same way that the "insane" are committed, which constitutes essentially an indeterminate sentence. The length of treatment should be controlled by the psychiatrist.

I doubt whether there is a hospital for mental disease that does not have some patients of this type. I believe that in each of the veterans' hospitals there are a few. These persons should be subjected to much the same conditions as are patients with psychoses; otherwise, the problem will not be met satisfactorily. A suitable institution should be well out in the country and equipped to take care of the most vicious, as well as those who are not vicious. It seems to me that the problem is one for a psychiatrist and one in which the psychiatric point of view should prevail.

DR. LOUIS H. ROBINSON: The psychiatrists should state more clearly what should be done with the psychopathic persons who are now in prison. Should there be a separate institution for them? If not, what provision should be made for them in the regular prisons?

There seems to be a move toward a clearcut policy in handling defective delinquent persons—those of low grade mentality. New York has provided separate institutions for them and has, I believe, arranged to send them to these institutions under a real indeterminate sentence, one with no maximum limit to it. Can one select another class of prisoners, those with psychopathic personalities, who would be acknowledged by competent psychiatrists as constituting a distinct class for whom special treatment should be devised? As a layman deeply interested in remaking the penal and correctional institutions, I should like more light on this difficult subject. Prison administrators and public men now wish to know what they should do, and it is time to formulate a practical program which, if not perfect, is a workable one for statesmen to follow.

DR. BALDWIN L. KEYES: If one could answer Dr. Robinson's question one would have gone a long way toward solving the problem with reference to psychopathic delinquency. All are agreed that the handling of the psychopathic patient as "insane" is by far the simplest and best method of control, which seems to be in the direction of indeterminate sentence, with the privilege of retaining the patient until cured. This means that the known "repeater" must remain always in an institution. Such methods, however, are impossible at this time, owing to the large number of such persons and the present state of underdevelopment for their proper care.

DETROIT SOCIETY OF NEUROLOGY AND PSYCHIATRY

H. A. REYE, M.D., *in the Chair*

Regular Meeting, March 24, 1938

FOURTEEN YEARS' EXPERIENCE WITH MALARIA IN TREATMENT OF DEMENTIA PARALYTICA. DR. W. H. SQUIRES, Eloise, Mich.

Malarial therapy was started at the Eloise Hospital for Mental Diseases on May 5, 1926. From then until Jan. 1, 1938, 752 male patients received malarial treatment. Of the 752 patients, 201 remain in the hospital; 288 have died; 60 have been transferred to other institutions, and 203 have been paroled. A patient

from each of two groups, those who have been on continuous parole outside the institution and those who have remained in the institution, is shown for each year from 1926 to 1937, inclusive. The 2 patients from each year are selected for the similarity in regard to positive psychiatric and neurologic findings, serologic reactions and the number of malarial paroxysms. Of the two contrasting groups, one showed progressive improvement, and the other, progressive deterioration or arrest without improvement. These contrasting results obtained under parallel conditions are offered for the purpose of inviting discussion of the prognostic criteria in dementia paralytica. It may be concluded from this series that the results are not predictable.

CLINICAL SYMPOSIUM: RECENT ADVANCES IN TREATMENT OF SCHIZOPHRENIA. DRS. L. S. LIPSCHUTZ, E. N. HINKO, R. LEISER and R. W. CAVELL, Eloise, Mich.

The use of insulin and metrazol in treatment of schizophrenic patients is briefly discussed, and the experiences with 30 patients receiving metrazol and 18 who have received or are receiving insulin are reported. The role of shock therapy in psychiatry is reviewed, and the various theories regarding the action of insulin are mentioned. The opinion is expressed that production of insulin hypoglycemia constitutes essentially a nonspecific shock therapy, the psychologic effects of which are at least as important as the physiologic. The advantages of hypoglycemic shock as compared with other forms of shock treatment are, first, the ease of reversal by administration of dextrose or sugar and, second, the facility with which the intensity of the shock may be regulated. The therapeutic value of increased attention inherent in the hypoglycemic treatment is emphasized, although it is pointed out that in cases used as controls, in which hypoglycemia was not induced, increased attention did not produce as much improvement as when combined with hypoglycemia.

The metrazol convulsion, as observed with 100 injections of the drug, occurred in 66 per cent of cases, the average dose being 5 cc. of a 10 per cent solution and the average duration of the convulsion fifty-seven seconds. No evaluation of the results is attempted, owing to the short span of treatment of the group of 30 patients.

Two motion picture films are shown. The first deals chiefly with the physiologic effects of insulin and the clinical manifestations of the hypoglycemic reaction. Included are observations on the alterations in metabolism, transient changes in the electrocardiogram and biochemical findings. The second film illustrates the therapeutic application of hypoglycemic shock in a group of 6 women with chronic schizophrenia. It shows patients before treatment, describes the routine in the ward necessary for carrying out the treatment and outlines the various indications and contraindications for this therapy. The film also displays patients in the various phases of hypoglycemic shock and illustrates the occupational and recreational activities employed as adjuncts to the treatment. Of the 6 patients, with a psychosis of from three to nine years' duration, 2 demonstrated remission to a level of full social adjustment and were accordingly paroled. A third displayed remission to a degree of social adjustment with moderate supervision. Another showed improvement to a degree of more adequate institutional adjustment. Two patients showed no improvement.

It is concluded that hypoglycemic shock therapy is worth while, that with proper facilities and organization it may be carried on without undue risk and that it is most effective when combined with a full range of occupational and recreational activity.

Book Reviews

Die **Insulin Shockbehandlung der Schizophrenie.** By DR. A. VON BRAUMÜHL. Price, 7.50 marks. Pp. 71. Berlin: Julius Springer, 1938.

This booklet is meant to be a practical guide to the management of the patient during hypoglycemia. Within the small space of seventy-one pages, it furnishes a wealth of material and deals rather exhaustively with the technical details of insulin shock therapy. This is the more remarkable because a considerable portion of the seventy-one pages is given over to nineteen tables and illustrations, four of them of full page size. The diction is plain and concise and renders the book available for any one moderately familiar with the German language.

A serious defect of the book is its dogmatic statement of rules in a field in which the gathering of reliable experience has merely begun. One rule, justification for which is not mentioned, decrees that the first hypoglycemic shock must not be allowed to last longer than from ten to fifteen minutes. Another rule declares, with no more show of authorization, that the hypoglycemia should never be extended beyond the fourth hour. At the end of the fourth hour it must be interrupted by the administration of "170 Gm. of cane sugar dissolved in 0.375 liter of weak tea" (page 17). The early epileptic fit is also interrupted with 170 Gm. of cane sugar. But the late epileptic fit requires 200 Gm., "i. e., 30 Gm. of sugar more than the early epileptic fit." The data of observation from which these stringent directions are drawn are not given, nor are the results tabulated which were obtained by means of the minutely described procedure.

The author recommends Georgi's method of combining insulin hypoglycemia with metrazol paroxysms. Here again he details instructions about procedure. Twenty comas are first produced with insulin; then follow from two to four successive days of metrazol therapy; a series of from ten to fifteen days of insulin treatment is then added, and the cycle is concluded with a few days of treatment with metrazol. The rationale of the method is not discussed; comparable results from alternative series are not given. The rule is merely dictated.

The book demonstrates once more the nonchalance with which in the domain of shock treatments arbitrary conclusions are drawn from scant and insufficiently digested experience. Whether the time has come for the elaboration of set rules for the management of treatment with insulin and metrazol is debatable. However, if an attempt is made it should be guided by the humble realization that both the obscurity of mental disease and the complexity of insulin shock command great caution.

The **Mentally Ill in America.** By ALBERT DEUTSCH. Price, $3. Pp. 530. New York: Doubleday Doran & Company, 1937.

Written simply, from the point of view of the social historian rather than of the psychiatrist, Mr. Deutsch's contribution not merely relates the specialist to the roots of his profession but orients him in the present scene in relation to the scientific controversy as one aspect of social processes. The slow and irregular reification of ideas amid conflicts of interests, the influence of individual personalities on mass indifference, the reaction after attainment of some moderately enlightened objective, subsequently to be rebelled against, appear in these five hundred pages as manifestations of the living, struggling, social organism.

The present scene, with many parts of the country lagging far behind available knowledge and others with procedures and provisions long established, emerges as the mosaic of the cultural, social and economic history of the nation. The

influences on the treatment accorded the mentally ill not only of economics and politics but also of the rise and pressure of various groups on each other within the medical profession itself (e. g., neurologists versus medical superintendents after the Civil War) are reflected in the final emergence of the psychiatric specialty in the present generation. The interaction of attitudes in the Old World with those in the New, from colonial days to the present day of insulin therapy, psychoanalysis and fever treatment, makes complete the dramatic story, given in a thoroughly documented account, and leads to a sober and fuller realization of the pressing problems now facing the infant specialty.

An appendix with an extensive bibliography and citations separated according to chapters and a detailed index add much to the value of the book as a source of reference, which should be on the reading list of every student in the field.

Safeguarding Mental Health. By RAPHAEL C. MCCARTHY, S.J., PH.D. Cloth. Price, $2.50. Pp. 297. Milwaukee: The Bruce Publishing Company, 1937.

Written in a popular style for "the average reader who has an interest in the subject of mental health, but who lacks formal training in psychology or psychiatry," this volume has little of interest for the student or specialist in the field. The author attempts a synthesis of modern principles of child guidance and the theological concepts of his church. Nevertheless, the essentially biologic concepts of heredity, environment and the present day psychiatric concepts of the psychoneuroses and psychoses are accurately rendered in a simple, readable style.

News and Comment

FELLOWSHIPS IN PSYCHOANALYSIS

The Boston Psychoanalytic Institute announces three Sigmund Freud Fellowships in psychoanalytic training, to begin in September 1939. The fellowships are open to graduates of a class A medical school who have had at least one year of general hospital training and two years' work in psychiatry. Applications must be made before Feb. 1, 1939. Further information may be obtained from Dr. M. Ralph Kaufman, chairman of the Educational Committee, 82 Marlborough Street, Boston.